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(54)【発明の名称】　アルデヒド誘導体

(57)【要約】　　（修正有）

【構成】一般式

$$R^4-\underset{\displaystyle R^3}{N}-\underset{\displaystyle R^2}{CH}-CONH-\underset{\displaystyle CHO}{CH}-(CH_2)_n-X-R^1 \quad (I)$$

〔例えば、L－N－ベンジルオキシカルボニルロイシン－（２Ｓ）－（１－ホルミル－２－ベンジルオキシ）エチルアミド〕で表されるアルデヒド誘導体である。

【効果】この化合物は、カルパインの阻害活性作用を有し、且つ血小板凝集作用を有するため、カルパインの活性異常により起こると考えられる虚血性疾患治療剤として有用である。

Applicant: Silviu Itescu
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Exhibit 2

1　　　　2

【特許請求の範囲】

【請求項１】一般式

【化１】

$$R^4-\overset{\overset{\displaystyle R^3}{|}}{N}-\overset{\overset{\displaystyle R^2}{|}}{CH}-CONH-\overset{\overset{\displaystyle CHO}{|}}{CH}-(CH_2)_n-X-R^1$$

で表されるアルデヒド誘導体（式中、R^1 は芳香族炭化水素基、複素環基、置換アルキル基又は環状アルキル基、R^2 は、水素原子、アルキル基又は芳香族炭化水素基、R^3 は、水素原子又はアルキル基、R^4 は、アルコ＊キシカルボニル基、アシル基、カルバモイル基、スルホニル基、Ｘは、酸素原子又は－Ｓ（Ｏ）$_m$－で表される基、ここでｍは０，１又は２であり、ｎは、１～５である。）。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、一般式

【０００２】

【化２】

$$R^4-\overset{\overset{\displaystyle R^3}{|}}{N}-\overset{\overset{\displaystyle R^2}{|}}{CH}-CONH-\overset{\overset{\displaystyle CHO}{|}}{CH}-(CH_2)_n-X-R^1 \qquad (\mathrm{I})$$

【０００３】（式中、R^1 は芳香族炭化水素基、複素環基、置換アルキル基又は環状アルキル基、R^2 は、水素原子、アルキル基又は芳香族炭化水素基、R^3 は、水素原子又はアルキル基、R^4 は、アルコキシカルボニル基、アシル基、カルバモイル基又はスルホニル基、Ｘは、酸素原子又は－Ｓ（Ｏ）$_m$－で表される基、ここでｍは０，１又は２であり，ｎは、１～５である。）で表されるアルデヒド誘導体に関する。前記一般式（Ｉ）で表されるアルデヒド誘導体は、カルパイン阻害活性及び血小板凝集抑制作用を有し虚血性疾患治療剤として用いることのできる化合物である。

【０００４】

【従来の技術】カルパインは、広く生体内組織の細胞内に存在し、カルシウムによって活性化される蛋白質分解酵素（システインプロテアーゼ）である。カルパインは、筋蛋白質、酵素蛋白質、レセプター蛋白質あるいは細胞骨格蛋白質等を基質とする組織崩壊、不活性酵素前駆体の活性化、細胞内プロセッシング等の生理活性を有することが知られている（蛋白質　核酸　酵素，第３３巻，１２号，２１７５（１９８８））。

【０００５】このカルパインの活性亢進によって引き起こされるカルパインの活性異常は、多くの難治性疾患に関与している。例えば虚血性疾患、炎症、筋ジストロフィー、白内障、免疫疾患、本態性高血圧等への関与が報告されている。特に虚血性疾患においては、虚血時の細胞内カルシウムの増加によってカルパインが活性化され、細胞障害、壊死を引き起こすと考えられている。

【０００６】従来この虚血性疾患の治療剤としては、カルシウム拮抗剤、β－ブロッカー等であり、血管を拡張する作用を有する薬剤が用いられてきた。しかしながら、これらの薬剤は、虚血性疾患において見られる細胞障害あるいは壊死を治療又は予防しうる効果を有するものではなかった。

【０００７】そこでカルパイン阻害剤はこれらの難治性疾患に対する治療剤として有用になる可能性がある。カルパイン阻害活性を有する化合物としては、既にエポキシコハク酸誘導体（Ｊ．Ｂｉｏｃｈｅｍ．，８７，３３９（１９８０）、ピペラジン誘導体（特開昭５７－１６９４７８号、特開昭５８－１２６８７９号、特開昭６３－２５５７５号）、アミノアルデヒド誘導体（特開昭６１－１０３８９７号、特開平１－１２１５７号、特開平２－２６８１４５号）、アミノアルデヒド、アミノケトン誘導体（特開平２－２５６６５４号）等が知られている。

【０００８】

【発明が解決しようとする課題】これらの化合物の中でピペラジン誘導体は、心筋保護作用を有することが報告され、虚血性疾患に対する治療剤としての可能性を有している。しかしながらこの誘導体は、カルパインへの阻害活性作用及び心筋保護の作用も低く充分な治療効果を期待できるものではなかった。また、このピペラジン誘導体以外の化合物においては、カルパインへの阻害活性を有するものの虚血性疾患に対する治療剤として用いることのできるものではなかった。

【０００９】

【課題を解決するための手段】そこで本発明者らは、虚血性疾患に有用なカルパイン阻害剤を見出すべく研究を行った結果、虚血性疾患の治療効果を高めるために血小板凝集抑制作用とカルパインへの特異的な阻害活性とを有する前記一般式（Ｉ）で表されるアルデヒド誘導体を見出し本発明を完成するに至った。

【００１０】前記一般式（Ｉ）で表わされるアルデヒド誘導体において、R^1 は芳香族炭化水素基、複素環基、置換アルキル基又は環状アルキル基である。この芳香族炭化水素基として、例えばフェニル基、ナフチル基、アントラニル基等、複素環基として例えばフリル基、チェニル基、ピロリル基、ピリジル基、キノリル基、イソキノリル基、インドリル基等、置換アルキル基として前記芳香族炭化水素基又は前記複素環基を置換基として有する炭素数１～１０の直鎖状及び分枝鎖状のアルキル基であり例えばメチル基、エチル基、プロピル基、ブチル基、ペンチル基、ヘキシル基、２－プロピル基、ｓｅｃ－ブチル基、ｔ－ブチル基等を挙げることができ、環状アルキル基として例えばシクロプロピル基、シクロブチ

ル基、シクロペンチル基、シクロヘキシル基等を挙げることができる。

【0011】さらに前記R^1の芳香族炭化水素もしくは複素環基、及び前記置換アルキル基の置換基である芳香族炭化水素基もしくは複素環基には、置換基を有していてもよく置換基として例えば、メチル基、エチル基、プロピル基、ブチル基等の炭素数１～１０のアルキル基、メトキシ基、エトキシ基、プロポキシ基、ブトキシ基、ベンジルオキシ基等の炭素数１～１０のアルコキシ基、フッ素、塩素、臭素、ヨウ素等のハロゲン基、アミノ基、ジメチルアミノ基、ジエチルアミノ基等のアミノ基、水酸基、ニトロ基等を挙げることができる。

【0012】R^2は、水素原子、直鎖状又は分枝鎖状のアルキル基又は芳香族炭化水素基である。このR^2のアルキル基としては炭素数１～１０の直鎖状又は分枝鎖状のアルキル基であり例えばメチル基、エチル基、プロピル基、イソプロピル基、ｎ－ブチル基、ｓｅｃ－ブチル基、イソブチル基、ｔ－ブチル基、ペンチル基、ネオペンチル基、ヘキシル基等を挙げることができ、芳香族炭化水素基としては、前記R^1で示した芳香族炭化水素基と同様な基を挙げることができる。さらにR^2のアルキル基には置換基を有していてもよく、置換基として例えば前記R^1で示した芳香族炭化水素基、複素環基を挙げることができる。

【0013】R^3は、水素原子又はアルキル基であり、アルキル基としては前記R^2と同様なアルキル基を挙げることができる。

【0014】R^4は、アルコキシカルボニル基、アシル基、カルバモイル基又はスルホニル基である。このアルコキシカルボニル基としては炭素数１～１０のアルコキシ基を有するアルコキシカルボニル基であり、例えばメトキシカルボニル基、エトキシカルボニル基、ｔ－ブトキシカルボニル基、シンナミルオキシカルボニル基、ベンジルオキシカルボニル基等を挙げることができ、アシル基としては、例えばアセチル基、プロピオニル基、ブチリル基、バレリル基、ベンゾイル基、１－ナフトイル基、２－ナフトイル基、シクロヘキサンカルボニル基、トルイル基、１－（ベンジルオキシカルボニル）ピペリジン－４－カルボニル基等を挙げることができ、カルバモイル基としては、例えばＮ－メチルカルバモイル基、Ｎ－エチルカルバモイル基、Ｎ－フェニルカルバモイル基、Ｎ－（２－クロロフェニル）カルバモイル基、Ｎ－（１－ナフチル）カルバモイル基、Ｎ－ベンジルカルバモイル基等を挙げることができ、さらに置換スルホニル基としては、例えばメタンスルホニル基、トリフルオロメタンスルホニル基、ベンゼンスルホニル基、４－メチルベンゼンスルホニル基、イソキノリン－５－スルホニル基、キノリン－８－スルホニル基等を挙げることができる。

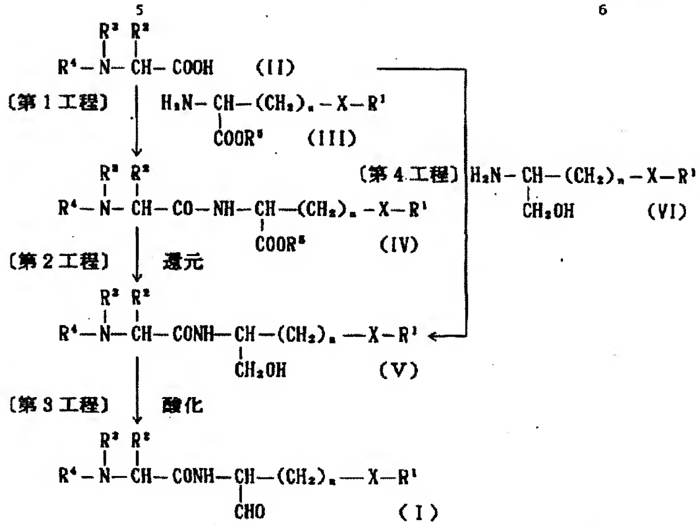
【0015】Xは酸素原子の他、$-S(O)_m-$で表わされる基でありここでmは0，1又は2である。nは1～5である。

【0016】前記一般式（Ｉ）で表わされるアルデヒド誘導体は例えば以下式Ｉに示す製造法に従い製造することができる。

【0017】式Ｉ

【0018】

【化3】



【0019】（式中、R^1，R^2，R^3，R^4，X、及びnは前記と同じであり、R^5 は炭素数1～15のアルキル基である。）

〔第1工程〕本工程は、前記一般式（II）で表わされるカルボン酸誘導体と前記一般式（III）で表わされるアミン誘導体とを縮合剤の存在下反応させることにより前記一般式（IV）で表わされるエステル誘導体を製造するものである。

【0020】前記一般式（III ）で表わされるアミン誘導体において、R^5 は炭素数1～15のアルキル基であり、例えばメチル基、エチル基、プロピル基、ブチル基、ベンジル基、ジフェニルメチル基等である。

【0021】本工程は、縮合剤の存在下行うことができ、縮合剤として例えばジシクロヘキシルカルボジイミド（DCC）、1－エチル－3－（3－ジメチルアミノプロピル）－カルボジイミド塩酸塩（WSC・HCl）等のカルボジイミド試薬等を挙げることができる。

【0022】本工程に用いる縮合剤は、前記一般式（II）で表わされるカルボン酸誘導体又は前記一般式（III ）で表わされるアミン誘導体1モルに対して1～3当量、収率よく製造するためには1．5～2当量用いることが好ましい。反応は、不活性溶媒中行なうことが望ましく例えば、ジクロロメタン、クロロホルム、ジクロロエタン等のハロゲン化炭化水素類、ベンゼル、トルエン、キシレン等の芳香族炭化水素類、ジエチルエーテル、ジメトキシエタン、テトラヒドロフラン（THF）、ジオキサン等のエーテル類、ジメチルホルムアミド（DMF）等のアミド類、ジメチルスルホキシド（DMSO）、アセトニトリル等を単独又は混合して使用することができる。反応は常圧下通常－50℃～還流温度で進行するが、収率よく実施するためには－30℃～30℃で行うことが好ましい。

【0023】なお、本工程の出発原料である前記一般式（II）で表わされるカルボン酸誘導体は、市販のアミノ酸誘導体又は市販のアミノ酸のアミノ基を前記R^3 及びR^4で表わされる基に変換して製造したものである。（後記参考例参照）。

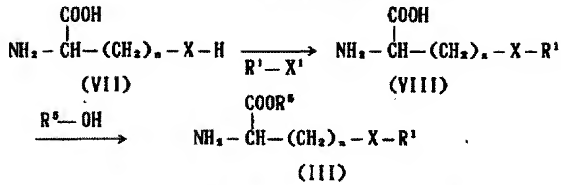
【0024】本発明で用いられる前記一般式（II）で表わされるカルボン酸誘導体としては、例えば、L－N－〔1－（ベンジルオキシカルボニル）ピペリジン－4－カルボニル〕ロイシン、L－N－（N－フェニルカルバモイル）ロイシン、L－N－（4－メチルベンゼンスルホニル）ロイシン、L－N－メチル－N－（ベンジルオキシカルボニル）ロイシン、L－N－（シンナモイル）ロイシン、L－N－（2－ナフトイル）ロイシン、L－N－（ベンジルオキシカルボニル）バリン、L－N－（ベンジルオキシカルボニル）フェニルアラニン等を挙げることができる。

【0025】また、本工程の出発原料である前記一般式（III ）で表わされるアミン誘導体は、市販のアミノ酸エステルを使用できる他、例えば下記式2に示す反応式に従い一般式（VII ）で表わされるアミノ酸より製造することができる。

【0026】式2

【0027】

＊ ＊【化4】



【0028】（式内、R^1，R^5，X及びnは前記と同じ基であり、X^1 はハロゲン原子である）。

【0029】さらに式2に示す前記一般式（III）で表わされるアミン誘導体は、必要に応じ前記一般式（VII）で表わされるアミノ酸のアミノ基をペプチド合成で用いられるアミノ基の保護基により、保護した後製造することもできる。

【0030】本工程で用いられる前記一般式（III）で表わされるアミン誘導体としては例えばL－O－（ベンジル）セリンエチルエステル、L－S－（2－フェニルエチル）システインメチルエステル、L－S－（3－フェニルプロピル）システインメチルエステル、L－O－（3－フェニルプロピル）セリンエチルエステル、L－O－（3－チエニルメチル）セリンエチルエステル、L－S－（ジフェニルメチル）システインメチルエステル、L－S－（シクロヘキシルメチル）システインエチルエステル、L－S－（シクロペンチル）システインエチルエステル、L－S－（2－チエニルメチル）システインメチルエステル、L－S－（3－チエニルメチル）システインエチルエステル、L－S－（1－ナフチルメチル）システインエチルエステル、L－S－（2－ナフチルメチル）システインエチルエステル、L－S－（2－クロロベンジル）システインエチルエステル等を挙げることができる。

【0031】また、本工程において、前記一般式（IV）で表わされるエステル誘導体は、前記一般式（II）で表わされるカルボン酸誘導体のカルボキシル基を例えば活性エステル化合物、カルボン酸ハライド化合物、酸無水物等に変換した後この第1工程と同様な不活性溶媒中前記一般式（III）で表わされるアミン誘導体の存在下に反応することにより製造することができる。

【0032】〔第2工程〕本工程は、前記一般式（IV）で表わされるエステル誘導体を還元し、前記一般式（V）で表わされるアルコール誘導体を製造するものである。

【0033】本工程を実施するための還元剤としては、例えば水素化ホウ素ナトリウム、水素化ホウ素リチウム等のホウ素化合物を挙げることができる。

【0034】還元剤の使用量は、前記一般式（IV）で表わされるエステル誘導体1モルに対し1～4当量用いることができる。反応は不活性溶媒中実施することが好ましく例えば、水、メタノール、エタノール等のアルコール類、エーテル、THF、ジメトキシエタン、ジオキサン等のエーテル類、ジクロロメタン、クロロホルム、ジクロロエタン等のハロゲン化炭化水素類、ベンゼン、トルエン、キシレン等の芳香族炭化水素類を単独又は混合して用いることができる。反応は－20℃～50℃で実施することができる。

【0035】〔第3工程〕本工程は、前記一般式（V）で表わされるアルコール誘導体を酸化し、前記一般式（I）で表わされるアルデヒド誘導体を製造するものである。本工程を実施するための酸化方法は、活性ジメチルスルホキシド（DMSO）酸化法であり、DMSO及びDMSOの活性化剤としてジシクロヘキシルカルボジイミド、五酸化リン、ピリジン－三酸化イオウ錯体、塩化オキザリル、無水酢酸、無水トリフルオロ酢酸等を用いることができる。酸化剤の使用量は、前記一般式（V）で表わされるアルコール誘導体1モルに対して、1～4当量用いることができる。

【0036】反応は、不活性溶媒中実施することが好ましく、例えばジクロロメンタン、ジクロロエタン、クロロホルム等のハロゲン化炭化水素類、DMSO等を用いることができる。反応は－20℃～30℃で実施することができる。

【0037】〔第4工程〕本工程は、前記一般式（II）で表わされるカルボン酸誘導体と、前記一般式（VI）で表わされるアミノアルコール誘導体とを縮合剤の存在下反応させることにより前記一般式（V）で表わされるアルコール誘導体を製造するものである。

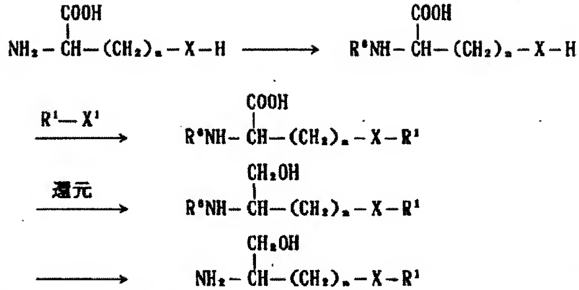
【0038】本工程は、第1工程と同様の縮合剤、反応条件、反応溶媒を用いて実施することができる。

【0039】本工程の原料である前記一般式（VI）で表わされるアミノアルコール誘導体は、例えば前記一般式（VII）で表わされるアミノ酸より式3に示す反応式に従い製造することができる。

【0040】式3

【0041】

【化5】



【0042】（式中、R^1，X，nは前記と同じであり、R^8は、アミノ基の保護基である。）本工程で用いられる前記一般式（VI）で表わされるアミノアルコール誘導体としては例えば（2R）−2−アミノ−3−（2−フルオロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（3−クロロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（4−クロロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（3−フルオロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（2−メトキシベンジルチオ）プロパノール、（2R）−2−アミノ−3−（3−フルオロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（3−メトキシベンジルチオ）プロパノール、（2R）−2−アミノ−3−（4−メトキシベンジルチオ）プロパノール、（2R）−2−アミノ−3−（3−ニトロベンジルチオ）プロパノール、（2R）−2−アミノ−3−（4−ニトロベンジルチオ）プロパノール、（2S）−2−アミノ−4−フェノキシブタノール、（2S）−2−アミノ−4−（フェニルチオ）ブタノール、（2S）−2−アミノ−3−（2−クロロベンジルオキシ）プロパノール、（2S）−2−アミノ−4−（2−フルオロフェノキシ）ブタノール、（2S）−2−アミノ−4−（3−フルオロフェノキシ）ブタノール、L−2−アミノ−4−（2−クロロフェノキシ）ブタノール、（2S）−2−アミノ−4−（3−クロロフェノキシ）ブタノール、（2S）−2−アミノ−4−ベンジルチオブタノール、（2S）−2−アミノ−4−（2−フルオロベンジルチオ）ブタノール、（2S）−2−アミノ−4−（2−クロロベンジルチオ）ブタノール、（2S）−2−アミノ−4−（2−フルオロフェニルチオ）ブタノール、（2S）−2−アミノ−4−（2−クロロフェニルチオ）ブタノール、（2S）−2−アミノ−4−（4−クロロフェニルチオ）ブタノール、（2S）−2−アミノ−4−（2−クロロベンジルオキシ）ブタノール、（2S）−2−アミノ−4−（2−フルオロベンジルオキシ）ブタノール、（2S）−2−アミノ−4−（3−ニトロベンジルオキシ）ブタノール等を挙げることができる。

【0043】また、本工程の出発原料である前記一般式（II）で表わされるカルボン酸誘導体は、前記第1工程と同様に、例えば活性エステル化合物、カルボン酸ハライド化合物、酸無水物等に変換した後、前記一般式（V）で表わされるアルコール誘導体として製造することもできる。

【0044】本工程により製造された前記一般式（V）で表わされるアルコール誘導体は、前記第3工程に従い、前記一般式（I）で表わされるアルデヒド誘導体を製造することができる。

【0045】

【作用】本発明の前記一般式（I）で表わされるアルデヒド誘導体は、試験例に示す通り、トリプシン、α−キモトリプシン等のプロテアーゼに対する阻害作用を持たずいずれも優れた特異的なカルパイン活性阻害作用、さらには血小板凝集抑制作用を有するため、虚血性疾患の治療に有用である。これらの化合物は、経口投与以外に、静脈内、皮下又は筋肉内に投与し得る。そのためにこれらの化合物は、種々の投与形態、例えば錠剤、カプセル、液体又は坐薬等の形で使用することができる。

【0046】

【実施例】本発明を以下の参考例、実施例及び試験例に従いさらに詳細に説明する。

【0047】（参考例1）L−O−（ベンジル）セリンエチルエステル塩酸塩（化合物（1））

L−N−（t−ブトキシカルボニル）−O−（ベンジル）セリン25g（8．5mmol）のエタノール溶液に濃塩酸1ml加え室温で2時間攪拌した。反応溶液減圧下溶媒留去し、得られた残留物のエタノール溶液に塩化チオニル1．3ml（17mmol）を加え室温で一夜攪拌した。反応溶液を減圧下溶媒留去し標記化合物（1）2．01g（収率91．6%）を得た。

【0048】NMR（δ，CD_3OD）：7.30-7.36(m,5H),4.59(dd,J=31.74Hz,J=12.15Hz,2H),4.24-4.31(m,3H),3.93(dd,J=10.53Hz,J=4.29Hz,1H),3.82(dd,J=10.65Hz,J=3.33Hz,1H),1.27(t,J=7.17Hz,3H)

（参考例2）Ｌ－Ｓ－（2－フェニルエチル）システインメチルエステル塩酸塩（化合物（2））

システイン塩酸塩水和物4．85ｇ（29．28mmol）を氷冷下ナトリウムメトキシド4．74ｇのメタノール溶液200mlに加え室温にて1時間攪拌した。反応溶液に2－ブロモエチルベンゼン5．55ｇ（30mmol）のメタノール溶液を滴下し氷冷下1時間攪拌した。溶媒を減圧下留去し得られた残留物を水に溶かしジエチルエーテルで洗浄、水層を濃塩酸で中性とした。析出した結晶を濾取し水、エタノール、ジエチルエーテルで洗浄し乾燥後Ｌ－Ｓ－フェニルエチルシステイン5．37ｇ（収率85．9%）を得た。得られた上記化合物5．3ｇ（23．5mmol）のメタノール溶液（200ml）とし氷冷下塩化チオニル8．6mlを滴下し滴下後反応溶液を室温とし一夜攪拌した。減圧下溶媒留去し得られた結晶をジエチルエーテルで洗浄し乾燥後標記化合物（2）6．27ｇ（収率96．3%）を得た。

【0049】NMR（δ，CD$_3$OD）：7.20-7.31(m,5H),4.25(dd,J=7.26Hz,J=4.23Hz,1H),3.83(s,3H),3.12(dd,J=14.49Hz,J=4.23Hz,1H),3.00(dd,J=14.54Hz,J=7.27Hz,1H),2.82-2.94(m,4H)

（参考例3）Ｌ－Ｓ－（3－フェニルプロピル）システインメチルエステル塩酸塩（化合物（3））

参考例2に準じてシステイン塩酸塩水和物4．85ｇ（29．28mmol）ナトリウムメトキシド4．75ｇ（87．84mmol）、3－ブロモプロピルベンゼン5．97ｇ（30mmol）、塩化チオニル6．7mlを用いて標記化合物（3）5．196ｇを得た。

【0050】NMR（δ，CD$_3$OD）：7.16-7.30(m,5H),4.27(dd,J=6.57Hz,J=4.18Hz,1H),3.82(s,3H),3.15(dd,J=14.54Hz,J=4.18Hz,1H),3.03(dd,J=14.49Hz,J=7.54Hz,1H),2.73(t,J=7.33Hz,2H),2.58(t,J=7.54Hz,2H),1.86-1.97(m,2H)

（参考例4）Ｌ－Ｏ－（3－フェニルプロピル）セリンエチルエステル塩酸塩（化合物（4））

Ｌ－Ｎ－（ｔ－ブトキシカルボニル）セリン3ｇ（14．6mmol）の無水ジメチルホルムアミド溶液に氷冷攪拌下60%油性水素化ナトリウム1．28ｇ（32mmol）を加え、室温に戻し2時間攪拌後、3－ブロモプロピルベンゼン3．18ｇ（16mmol）を加え一夜攪拌した。反応溶液を減圧下濃縮し残留物水に溶かしジエチルエーテルで洗浄し、水層を1Ｎ－塩酸水溶液で酸性とし酢酸エチルで抽出し、有機層を水で洗浄し無水硫酸ナトリウムで乾燥し減圧下溶媒留去し得られた残留物をエタノールに溶かし濃塩酸を加え一夜攪拌後塩化チオニル4ml加え一夜攪拌した。減圧下溶媒留去し得られた結晶をジエチルエーテルで洗浄し乾燥後標記化合物（4）1．13ｇを得た。

【0051】NMR（δ，CD$_3$OD）：7.15-7.28(m,5H),4.32(q,J=6.52Hz,2H),4.25(t,J=1.68Hz,1H),3.92(dd,J=10.91Hz,J=4.40Hz,1H),3.82(dd,J=10.04Hz,J=2.82Hz,1H),3.44-3.59(m,2H),2.67(t,J=7.32,2H),1.85-1.95(m,2H),1.32(t,J=7.49,3H)

（参考例5）Ｌ－Ｏ－（チオフェン－3－イルメチル）セリンエチルエステル塩酸塩（化合物（5））

参考例4に準じＬ－Ｂｏｃ－Ｓｅｒ－ＯＨ40ｇ（19．5mmol）60%油性水素化ナトリウム172ｇ（43mmol）、3－ブロモメチルチオフェン4．44ｇ（25mmol）、濃塩酸2．2ｇ及び塩化チオニル2．3mlを用いて標記化合物（5）1．25ｇを得た。

【0052】NMR（δ，CD$_3$OD）：7.36-7.42(m,2H),7.08-7.10(m,1H),4.60(q,J=12.21Hz,2H),4.27(q,J=7.11Hz,1H),4.21(t,J=3.18Hz,1H),3.90(dd,J=4.32Hz,J=9.87Hz,1H),3.81(dd,J=3.27Hz,J=10.47Hz,1H),1.27(t,J=7.11Hz,3H)

（参考例6）Ｌ－Ｓ－（ジフェニルメチル）システインメチルエステル塩酸塩（化合物（6））

Ｌ－システイン塩酸塩水和物3．0ｇ（17．1mmol）とジフェニルメタノール3．15ｇ（17．1mmol）をトリフルオロ酢酸40mlに加え室温で1時間攪拌した。減圧下トリフルオロ酢酸を留去し残留物にジエチルエーテルを加え結晶化し、水、エタノール、ジエチルエーテルで洗浄後減圧下乾燥させＬ－Ｓ－ジフェニルメチルシステイン5．2ｇ（収率～100%）を得た。得られた上記化合物1．0ｇ（3．5mmol）のメタノール溶液に氷冷下塩化チオニル1．0mlを滴下し滴下後反応溶液を室温に上げ一夜攪拌した。減圧下溶媒留去し得られた結晶をジエチルエーテルで洗浄して標記化合物（6）1．11ｇ（収率～100%）を得た。

【0053】NMR（δ，CDCl$_3$）：7.41-7.44(m,4H),7.15-7.29(m,6H),5.42(s,1H),4.22-4.32(m,1H),3.61(s,3H),2.98-3.03(m,2H),2.78-2.89(m,2H)

（参考例7）Ｌ－Ｓ－（シクロヘキシルメチル）システインエチルエステル塩酸塩（化合物（7））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりにシクロヘキシルメチルブロミドを用い標記化合物（7）を得た。

【0054】NMR（δ，CDCl$_3$）：4.35-4.39(m,1H),4.30(q,J=7.17Hz,2H),3.24(d,J=5.22Hz,2H),2.50(dd,J=6.90Hz,J=3.18,2H),2.20-2.65(m,2H),1.38-1.88(m,5H),1.33(t,J=14.28,J=7.17,3H),0.87-1.28(m,6H)

（参考例8）Ｌ－Ｓ－（シクロペンチル）システインエチルエステル塩酸塩（化合物（8））

参考例2に準じ2－ブロモエチルベンゼンのかわりにシクロペンチルブロミドを用い標記化合物（8）を得た。

【0055】NMR（δ，CD$_3$OD）：4.44(t,J=5.19Hz,1H),4.32(t,J=6.99Hz,2H),4.27-4.29(m,1H),3.31-3.46(m,4H),3.17(dd,J=17.19,J=4.77,1H),3.07(dd,J=13.91,J=6.99,1H),2.00-2.11(m,1H),1.72-1.81(m,1H),1.46-1.68(m,2H),1.35(t,J=7.20Hz,3H)

（参考例9）L－S－（チオフェン－2－イルメチル）システインメチルエステル塩酸塩（化合物（9））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりに2－クロロメチルチオフェンを用い標記化合物（9）を得た。

【0056】NMR（δ，CD$_3$OD）：7.34(dd,J=5.26Hz,J=1.36Hz,1H),7.04(d,J=4.56Hz,1H),6.95(dd,J=5.04Hz,J=1.62Hz,1H),4.22(dd,J=7.92Hz,J=4.5Hz,1H),4.06(d,J=3.31Hz,2H),3.84(s,3H),3.10(dd,J=14.81Hz,J=4.56Hz,1H),2.96(dd,J=14.92Hz,J=8.03Hz,1H)

（参考例10）L－S－（チオフェン－3－イルメチル）システインエチルエステル塩酸塩（化合物（10））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりに3－ブロモメチルチオフェンを用いて標記化合物（10）を得た。

【0057】NMR（δ，CD$_3$OD）：7.41(dd,J=4.95Hz,J=2.01Hz,1H),7.32(br,s,1H),7.12(d,J=4.89Hz,1H),4.29(q,J=7.26Hz,2H),4.14(dd,J=8.04Hz,J=3.57Hz,1H),3.87(s,2H),3.03(dd,J=14.76Hz,J=4.5Hz,1H),2.90(dd,J=14.82Hz,J=8.13Hz,1H),1.31(t,J=7.23Hz,3H)

（参考例11）L－S－（1－ナフチルメチル）システインエチルエステル塩酸塩（化合物（11））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりに1－ナフチルメチルブロミドを用いて標記化合物（11）を得た。

【0058】NMR（δ，CD$_3$OD）：8.18(d,J=8.37Hz,1H),7.80-7.90(m,2H),7.35-7.58(m,4H),4.33(s,2H),4.17-4.29(m,3H),3.04(dd,J=4.44Hz,J=9.72,1H),2.95(dd,J=7.80Hz,J=14.64Hz,1H),1.25(t,J=7.02Hz,3H)

（参考例12）L－S－（2－ナフチルメチル）システインエチルエステル塩酸塩（化合物（12））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりに2－ナフチルメチルブロミドを用いて標記化合物（12）を得た。

【0059】NMR（δ，CD$_3$OD）：7.81-7.88(m,4H),7.47-7.55(m,3H),4.21-4.25(m,2H),4.13-4.20(m,1H),4.00(s,2H),3.01(dd,J=9.78Hz,J=4.38Hz,1H),2.89(dd,J=8.19Hz,J=6.39Hz,1H),1.22(t,J=7.05Hz,3H)

（参考例13）L－S－（2－クロロベンジル）システインエチルエステル塩酸塩（化合物（13））

参考例2に準じた方法で2－ブロモエチルベンゼンのかわりに2－クロロベンジルクロリドを用い標記化合物（13）を得た。

【0060】NMR（δ，CD$_3$OD）：7.41-7.48(m,2H),7.28-7.31(m,2H),4.30(q,J=7.33Hz,2H),4.25-4.29(m,1H),3.12(dd,J=14.71Hz,J=4.45Hz,1H),2.97(dd,J=14.65Hz,J=7.86Hz,1H),1.31(t,J=7.16Hz,3H)

（参考例14）（2R）－2－アミノ－3（2－フルオロベンジルチオ）プロパノール（化合物（14））

金属ナトリウム12．0g（519mmol）とメタノール700mlより調製したナトリウムメトキシドのメタノール溶液にL－システイン塩酸塩・水和物30．4g（173mmol）を加えた。次いで2－フルオロベンジルクロリド25．0g（173mmol）を滴下し、さらに室温で一夜攪拌した。減圧下メタノールを留去して得られた残留物を水に溶かしエーテルで2回洗浄後濃塩酸を加え（pH＝7）、析出した結晶を濾取し水、エタノール次いでジエチルエーテルで洗浄し減圧下乾燥させ（2R）－2－アミノ－3（2－フルオロベンジルチオ）プロピオニックアシド29．7g（収率74．8%）を得た。水素化ホウ素リチウム0．58g（26．4mmol）の無水テトラヒドロフラン溶液にクロロトリメチルシラン6．7ml（52．8mmol）を加え室温で30分攪拌した。その混合溶液に（2R）－2－アミノ－3（2－フルオロベンジルチオプロピオニックアシド2．02g（8．8mmol）を加え室温で一夜攪拌した。反応溶液にメタノールを加え減圧下溶媒留去した。得られた残留物を1N－水酸化ナトリウム水溶液に溶かしクロロホルムにて抽出した。無水硫酸ナトリウムで乾燥後、減圧下溶媒留去し標記化合物（14）1．69g（収率89．4%）を得た。

【0061】NMR（δ，CDCl$_3$）：7.19-7.36(m,2H),7.00-7.12(m,2H),3.75(s,2H),3.65(dd,J=10.86Hz,J=3.78Hz,1H),3.42(dd,J=10.74Hz,J=6.45Hz,1H),3.00-3.10(m,1H),2.80(br,s,3H),2.62(dd,J=13.56Hz,J=4.92Hz,1H),2.45(dd,J=13.35Hz,J=8.22Hz,1H)

（参考例15）（2R）－2－アミノ－3（3－クロロベンジルチオ）プロパノール（化合物（15））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに3－クロロベンジルブロミドを用い標記化合物（15）を得た。

【0062】NMR（δ，CDCl$_3$）：7.15-7.35(m,4H),3.68(s,2H),3.64(d,J=3.52Hz,1H),3.44(dd,J=6.45Hz,J=10.85Hz,1H),2.98(br s,4H),2.60(dd,J=5.21Hz,J=13.4Hz,1H),2.45(dd,J=8.08Hz,J=13.45Hz,1H)

（参考例16）（2R）－2－アミノ－3（4－クロロベンジルチオ）プロパノール（化合物（16））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに4－クロロベンジルクロリドを用い標記化合物（16）を得た。

【0063】NMR（δ，CDCl$_3$）：7.26(q,J=8.52,4H),3.68(s,2H),3.60(dd,J=4.02Hz,J=10.75Hz,1H),3.38(dd,J=6.46Hz,J=10.8Hz,1H),2.96(br s,1H),2.54(dd,J=4.77Hz,J=13.18Hz,1H),2.36(dd,J=8.25Hz,J=13.35Hz,1H),2.24(br s,3H)

（参考例17）L－2－アミノ－3（3－フルオロベンジルチオ）プロパノール（化合物（17））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに3－フルオロベンジルクロリドを用い標記

化合物（17）を得た。

【0064】NMR（δ，CDCl₃）：7.21〜7.28(m,1H),6.89〜7.10(m,3H),4.76(s,3H),3.76(dd,J=3.42Hz,J=11.5Hz,1H),3.72(s,2H),3.57(dd,J=7.82Hz,J=12.59Hz,1H),3.25(br s,1H),2.62(d,J=7.05Hz,2H)

（参考例18）（2R）－2－アミノ－3（4－フルオロベンジルチオ）プロパノール（化合物（18））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに4－フルオロベンジルクロリドを用い標記化合物（18）を得た。

【0065】NMR（δ，CDCl₃）：7.25〜7.30(m,2H),6.97〜7.03(m,2H),3.69(s,2H),3.60(dd,J=4.23Hz,J=10.74Hz,1H),3.37(dd,J=6.57Hz,J=10.74Hz,1H),2.95(brs,1H),2.55(dd,J=4.93Hz,J=13.29Hz,1H),2.01(brd,J=10.25Hz,3H),2.36(dd,J=8.31Hz,13.30Hz,1H)

（参考例19）（2R）－2－アミノ－3（2－メトキシベンジルチオ）プロパノール（化合物（19））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに2－メトキシベンジルクロリドを用い標記化合物（19）を得た。

【0066】NMR（δ，CDCl₃）：7.21〜7.26(m,2H),6.86〜6.94(m,2H),3.85(s,3H),3.74(s,2H),3.62(dd,J=10.74Hz,J=4.13Hz,1H),3.37(dd,J=10.74Hz,J=6.73,1H),2.97-3.05(m,1H),2.62(dd,J=13.51Hz,J=4.83Hz,1H),2.40(dd,J=13.57Hz,J=8.31Hz,1H),2.08(br s,3H)

（参考例20）（2R）－2－アミノ－3（3－メトキシベンジルチオ）プロパノール（化合物（20））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに3－メトキシベンジルクロリドを用い標記化合物（20）を得た。

【0067】NMR（δ，CDCl₃）：7.22(t,J=8.25,1H),6.88(d,J=6.68Hz,1H),6.86(s,1H),6.79(dd,J=2.06Hz,J=7.48Hz,1H),3.80(s,3H),3.68(s,2H),3.58(dd,J=4.18Hz,J=10.8Hz,1H),3.36(dd,J=6.62Hz,J=10.75Hz,1H),2.90〜3.00(m,1H),2.56(dd,J=4.88Hz,J=13.29Hz,1H),2.36(dd,J=8.19Hz,J=13.35Hz,1H),2.11(br s,3H)

（参考例21）（2R）－2－アミノ－3（4－メトキシベンジルチオ）プロパノール（化合物（21））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに4－メトキシベンジルクロリドを用い標記化合物（21）を得た。

【0068】NMR（δ，CDCl₃）：7.22(d,J=8.63Hz,2H),6.85(d,J=8.63Hz,2H),3.80(s,3H),3.67(s,2H),3.59(dd,J=4.13Hz,J=10.74Hz,1H),3.36(dd,J=6.62Hz,J=10.75Hz,1H),2.90〜2.98(m,1H),2.55(dd,J=4.88Hz,J=13.29Hz,1H),2.36(dd,J=8.24Hz,J=13.29Hz,1H),1.99(s,3H)

（参考例22）（2R）－2－アミノ－3（3－ニトロベンジルチオ）プロパノール（化合物（22））

参考例14に準じた方法で2－フルオロベンジルクロリドのかわりに3－ニトロベンジルクロリドを用い標記化合物（22）を得た。

【0069】NMR（δ，CDCl₃）：8.20(s,1H),8.13(d,J=8.24Hz,1H),7.67(d,J=7.75Hz,1H),7.51(t,J=7.87Hz,1H),3.81(s,2H),3.62(dd,J=10.75Hz,J=4.24Hz,1H),3.42(dd,J=10.75Hz,J=6.35Hz,1H),3.00-3.08(m,1H),2.58(dd,J=13.18Hz,J=4.94Hz,1H),2.41(dd,J=13.23Hz,J=8.13Hz,1H),2.05(br s,3H)

（参考例23）（2R）－2－アミノ－3（4－ニトロベンジルチオ）プロパノール（化合物（23））

L－システイン塩酸塩水和物5．27g（30mmol）を1N－水酸化ナトリウム水溶液に加え、次いで4－ニトロベンジルクロリド5．15g（30mmol）のジオキサン溶液を滴下して室温で1時間攪拌した。反応溶液をジエチルエーテル洗浄し、濃塩酸で弱酸性とし冷却したところ結晶が析出した結晶を濾過しエタノール次いでジエチルエーテル洗浄し減圧下乾燥しL－2－アミノ－3（4－ニトロベンジルチオ）プロピオニックアシド3．55g（収率45．9%）を得た。アルコール体への変換反応は参考例14に準じた方法を用いて標記化合物（23）を得た。

【0070】NMR（δ，CDCl₃）：8.19(d,J=8.63Hz,2H),7.50(d,J=8.69Hz,2H),3.80(s,2H),3.60(dd,J=4.18Hz,J=10.74Hz,1H),3.40(dd,J=6.35Hz,J=10.74Hz,1H),2.92-3.02(m,1H),2.57(dd,J=4.94Hz,J=13.19Hz,1H),2.39(dd,J=8.13Hz,J=13.18Hz,1H),2.01(s,3H)

（参考例24）（2S）－2－アミノ－4－フェニルオキシブタノール塩酸塩（化合物（24））

（Tetrahedron Letters 20巻，2243，1978年の方法に従って合成した）L－N－（t－ブトキシカルボニル）－ホモセリンカリウム塩142g（0．59mol）の無水ジメチルホルムアミド溶液にエチルブロミド320g（2．94mol）を滴下して加え室温にて一夜攪拌した。減圧下溶媒留去して、得られた残留物を水にとかし酢酸エチルで抽出し飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥して、減圧下溶媒留去した。得られた残留物をシリカゲルカラムクロマトグラフィーにて精製しL－N－（t－ブトキシカルボニル）－ホモセリンエチルエステルを44．5g（収率31%）を得た。上記で得た化合物6．18g（25mmol）とトリエチルアミン3．04g（30mmol）の酢酸エチル溶液に氷冷攪拌下メタンスルホニルクロリド3．44g（30mmol）を加え1時間攪拌した。反応溶液を水洗し無水硫酸ナトリウムで乾燥後減圧下濃縮することによりメタンスルホナート体を8．12g（収率〜100%）を得た。フェノール0．88gの無水ジメチルホルムアミド溶液に60%油性水素化ナトリウム0．35gを加え1時間攪拌した後先の反応で得たメタンスルホナート体2．55g（7．83mmol）のジメチルホルムアミド溶液を滴下し室温で一夜攪拌した。反応溶液

に飽和NH$_4$Cl水を加え酢酸エチルで抽出し飽和炭酸水素ナトリウム水溶液、次いで水で洗浄した。無水硫酸ナトリウムで乾燥後溶媒留去し得られる残留物をシリカゲルカラムクロマトグラフィーで精製しL－N－（t－ブトキシカルボニル）－O－フェニルホモセリンエチルエステル2．13g（収率84％）を得た。

【0071】NMR（δ，CDCl$_3$）：7.20-7.30(m,2H),6.83-6.97(m,3H),5.34-5.42(m,1H),4.45-4.52(m,1H),4.18(q,J=7.22Hz,2H),4.04(t,J=6.08Hz,2H),2.20-2.37(m,2H),1.44(s,9H),1.25(t,J=7.06Hz,3H)

上記化合物2．10g（6．5mmol）のテトラヒドロフラン溶液に水素化ホウ素リチウム0．28g加え次いで冷却攪拌下メタノールを滴下し1時間攪拌した。反応溶液に水を加え減圧下溶媒留去し得られた残留物に1N－塩酸水溶液を加え酢酸エチルで抽出した。有機層を飽和炭酸水素ナトリウム水溶液次いで水で洗浄し無水硫酸ナトリウムで乾燥後減圧下溶媒留去した。得られた残留物を4N－塩酸酢酸エチルに溶解し1時間攪拌した。減圧下溶媒留去し標記化合物（24）0．64g（収率46％）を得た。

【0072】（参考例25）（2S）－2－アミノ－4－（フェニルチオ）ブタノール塩酸塩（化合物（25））

参考例24に準じた方法でエチルブロミドのかわりにベンジルブロミドを用い、フェノールのかわりにチオフェノールを用いてL－N－（t－ブトキシカルボニル）－S－フェニルホモシステインベンジルエステルを得た。

【0073】NMR（δ，CDCl$_3$）：7.16-7.37(m,10H),5.15(d,J=3.31Hz,2H),5.09-5.20(m,1H),4.47-4.53(m,1H),2.90(dt,J=6.3Hz,J=2.11,2H),2.10-2.20(m,1H),1.89-2.00(m,1H),1.43(s,9H)

更に参考例24に準じた方法で標記化合物（25）を得た。

【0074】（参考例26）（2R）－2－アミノ－3－（2－クロロベンジルオキシ）－プロパノール塩酸塩（化合物（26））

L－N－（t－ブトキシカルボニル）セリン7．0g（34mmol）の無水ジメチルホルムアミド溶液に60％油性水素化ナトリウム3．0gを加え室温で3時間攪拌した。次いで2－クロロベンジルクロリド6．0g（37mmol）を滴下し、室温で一夜攪拌した。溶媒を減圧下留去後得られる残留物を酢酸エチル－1N－塩酸混合溶媒に溶解し酢酸エチル層を水洗し、無水硫酸ナトリウムで乾燥後溶媒を留去することによりL－N－（t－ブトキシカルボニル）－O－（2－クロロベンジル）－セリン4．3g（収率38％）を得た。得られた上記化合物2．15g（6．5mmol）とトリエチルアミンのテトラヒドロフラン溶液に塩－氷で冷却しながらクロロ炭酸エチル0．93gを滴下し、2時間攪拌した。析出した結晶を濾過して除き濾液に氷冷攪拌下水素化ホウ素ナトリ

ウム次いでメタノールを滴下し2時間攪拌した。溶媒を減圧下留去し得られた残留物の水溶液に1N－塩酸水溶液を加え酢酸エチルで抽出した。有機層を10％水酸化ナトリウム水溶液次いで水洗浄し無水硫酸ナトリウムで乾燥後溶媒留去しシリカゲルカラムクロマトグラフィーで精製しアルコール体0．81gを得た。得られたアルコール体0．8gを4N－塩酸酢酸エチルに溶解し室温で30分間攪拌、溶媒を留去後標記化合物（26）0．55g（収率19％）を得た。

【0075】NMR（δ，CD$_3$OD）：7.53-7.56(m,1H),7.39-7.42(m,1H),7.30-7.35(m,2H),4.70(s,2H),3.67-3.82(m,4H),3.42-3.49(m,1H)

（参考例27）（2S）－2－アミノ－4－（2－フルオロフェニルオキシ）ブタノール塩酸塩（化合物（27））

参考例24に準じた方法でフェノールのかわりに2－フルオロフェノールを用いてL－N－（t－ブトキシカルボニル）－O－（2－フルオロフェニル）－ホモセリンエチルエステルを得た。

【0076】NMR（δ，CDCl$_3$）：6.85-7.10(m,4H),5.40-5.46(m,1H),4.42-4.51(m,1H),4.22(q,J=7.0Hz,2H),4.12(q,J=5.48Hz,2H),2.23-2.41(m,2H),1.44(s,9H),1.26(t,J=7.16Hz,3H)

更に参考例24に準じた方法で標記化合物（27）を得た。

【0077】（参考例28）（2S）－2－アミノ－4（3－フルオロフェニルオキシ）ブタノール塩酸塩（化合物（28））

参考例24に準じた方法でフェノールのかわりに3－フルオロフェノールを用いてL－N－（t－ブトキシカルボニル）－O－（3－フルオロフェニル）－ホモセリンエチルエステルを得た。

【0078】NMR（δ，CDCl$_3$）：7.11-7.24(m,1H),6.55-6.69(m,3H),5.31-5.38(m,1H),4.45-4.51(m,1H),4.20(q,J=7.16Hz,2H),4.03(t,J=6.02Hz,2H),2.20-2.38(m,2H),1.44(s,9H),1.26(t,J=7.11Hz,3H)

参考例24に準じた方法で標記化合物（28）を得た。

【0079】（参考例29）（2S）－2－アミノ－4（2－クロロフェニルオキシ）ブタノール塩酸塩（化合物（29））

参考例24に準じた方法でエチルブロミドのかわりにベンジルブロミドを用い、フェノールのかわりに2－クロロフェノールを用いてL－N－（t－ブトキシカルボニル）－O－（2－クロロフェニル）－ホモセリンベンジルエステルを得た。

【0080】NMR（δ，CDCl$_3$）：7.30-7.36(m,6H),7.18(dt,J=6.67Hz,J=1.6,1H),6.90(dt,J=6.3Hz,J=1.35Hz,1H),6.80(d,J=8.24Hz,1H),5.80-5.83(m,1H),5.18(d,J=2.17Hz,2H),4.55-4.62(m,1H),4.07-4.14(m,1H),3.95-4.00(m,1H),2.40-2.50(m,2H),1.43(s,9H)

更に参考例２４に準じた方法で標記化合物（２９）を得た。

【００８１】（参考例３０）（２Ｓ）－２－アミノ－４（３－クロロフェニルオキシ）ブタノール塩酸塩（化合物（３０））

参考例２４に準じた方法でエチルブロミドのかわりにベンジルブロミドを用い、フェノールのかわりに３－クロロフェノールを用いてＬ－Ｎ－（ｔ－ブトキシカルボニル）－Ｏ－（３－クロロフェニル）－ホモセリンベンジルエステルを得た。

【００８２】ＮＭＲ（δ，$CDCl_3$）：7.34(s,5H),7.16(t,J=8.14Hz,1H),6.92(dd,J=5.53Hz,J=1.96Hz,1H),6.80(s,1H),6.69(dd,J=6.35Hz,J=2.01,1H),5.25-5.30(m,1H),5.18(d,J=2.23Hz,2H),4.50-4.57(m,1H),3.98(t,J=5.96Hz,2H),2.25-2.37(m,2H),1.43(s,9H)

更に参考例２４に準じた方法で標記化合物（３０）を得た。

【００８３】（参考例３１）Ｌ－２－アミノ－４－ベンジルチオブタノール（化合物（３１））

－７８℃に冷却した液体アンモニアに金属ナトリウム１ｇを加え３０分間攪拌後反応溶液にホモシステイン２．０ｇ（７．４５mmol）を加えて３０分間攪拌した。反応溶液に反応液の青色が無くなるまで塩化アンモニウムを加え次いでベンジルブロミド０．６９ｇ（３０mmol）を加え室温で液体アンモニアを蒸発させる。得られた残留物を水に溶かしジエチルエーテルで洗浄し濃塩酸を加え弱酸性とし冷所で結晶を析出させた。得られた結晶を水、エタノール、エーテルで順次洗浄し減圧下乾燥させ（２Ｓ）－２－アミノ－４－ベンジルチオブタノイックアシド２．８ｇ（収率８６％）を得た。

【００８４】水素化ホウ素リチウム０．４９ｇ（２２mmol）の無水テトラヒドロフラン溶液にトリメチルシリロキシクロリド５．６ml（４４mmol）を加え室温で３０分攪拌した。その混合溶液に（２Ｓ）－２－アミノ－４－ベンジルチオブタノイックアシド２．５ｇ（１１mmol）を加え室温で一夜攪拌した。反応溶液にメタノールを加え減圧下溶媒留去した得られた残留物を１Ｎ－水酸化ナトリウム水溶液に溶かしクロロホルムにて抽出した。無水硫酸ナトリウムで乾燥後減圧下溶媒留去し標記化合物（３１）２．０ｇ（収率８５．５％）を得た。

【００８５】ＮＭＲ（δ，$CDCl_3$）：7.22-7.32(m,5H),3.72(s,2H),3.51-3.56(m,1H),3.26-3.30(m,1H),2.90-3.00(m,1H),2.42-2.58(m,2H),2.00-2.12(m,1H),1.62-1.73(m,1H),1.48-1.58(m,1H)

（参考例３２）（２Ｓ）－２－アミノ－４（２－フルオロベンジルチオ）ブタノール（化合物（３２））

参考例３１に準じた方法でベンジルブロミドのかわりに２－フルオロベンジルブロミドを用い標記化合物（３２）を得た。

【００８６】ＮＭＲ（δ，$CDCl_3$）：7.31-7.36(m,1H),7.19-7.27(m,1H),7.00-7.12(m,2H),3.75(s,2H),3.55(dd,J=10.68Hz,J=3.96Hz,1H),3.28(dd,J=13.59Hz,J=7.49Hz,1H),2.89-2.97(m,1H),2.47-2.62(m,2H),1.98(br s,3H),1.65-1.76(m,1H),1.49-1.59(m,1H)

（参考例３３）（２Ｓ）－２－アミノ－４（２－クロロベンジルチオ）ブタノール（化合物（３３））

参考例３１に準じた方法でベンジルブロミドのかわりに２－クロロベンジルクロリドを用い標記化合物（３３）を得た。

【００８７】ＮＭＲ（δ，$CDCl_3$）：7.33-7.39(m,2H),7.19-7.26(m,2H),3.84(s,2H),3.57(dd,J=10.69Hz,J=4.01Hz,1H),3.29(dd,J=10.69Hz,J=7.49Hz,1H),2.93-3.01(m,1H),2.50-2.66(m,2H),2.04(br s,3H),1.66-1.78(m,1H),1.50-1.62(m,1H)

（参考例３４）（２Ｓ）－２－アミノ－４（２－フルオロフェニルチオ）ブタノール塩酸塩（化合物（３４））

参考例２４に準じた方法でエチルブロミドのかわりにベンジルブロミドを用い、フェノールのかわりに２－フルオロチオフェノールを用いてＬ－Ｎ－（ｔ－ブトキシカルボニル）－Ｓ－（２－フルオロフェニル）ホモシステインベンジルエステルを得た。

【００８８】ＮＭＲ（δ，$CDCl_3$）：7.18-7.42(m,6H),7.01-7.07(m,2H),5.16(d,J=2.66Hz,2H),5.09-5.14(m,1H),4.45-4.53(m,1H),2.90(t,J=7.49Hz,2H),2.06-2.18(m,1H),1.86-1.98(m,1H),1.43(s,9H)

更に参考例２４に準じた方法で標記化合物（３４）を得た。

【００８９】（参考例３５）（２Ｓ）－２－アミノ－４（２－クロロフェニルチオ）ブタノール塩酸塩（化合物（３５））

参考例２４に準じた方法でエチルブロミドのかわりにベンジルブロミドを用いフェノールのかわりに２－クロロチオフェノールを用いてＬ－Ｎ－（ｔ－ブトキシカルボニル）－Ｓ－（２－クロロフェニル）ホモシステインベンジルエステルを得た。

【００９０】ＮＭＲ（δ，$CDCl_3$）：7.34(s,6H),7.08-7.23(m,3H),5.17(d,J=3.31Hz,3H),4.40-4.51(m,1H),2.90-2.96(m,2H),2.17-2.25(m,1H),1.95-2.05(m,1H),1.44(s,9H)

更に参考例２４に準じた方法で標記化合物（３５）を得た。

【００９１】（参考例３６）（２Ｓ）－２－アミノ－４（４－クロロフェニルチオ）ブタノール塩酸塩（化合物（３６））

参考例２４に準じた方法でエチルブロミドのかわりにベンジルブロミドを用い、フェノールのかわりに４－クロロチオフェノールを用いてＬ－Ｎ－（ｔ－ブトキシカルボニル）－Ｓ－（４－クロロフェニル）ホモシステインベンジルエステルを得た。

【００９２】ＮＭＲ（δ，$CDCl_3$）：7.29-7.37(m,

4H),7.21(s,5H),5.15(d,J=7.16Hz,2H),5.10-5.15(m,1H),4.12-4.19(m,1H),2.84-2.90(m,2H),2.05-2.18(m,1H),1.86-1.97(m,1H),1.43(s,9H)
更に参考例２４に準じた方法で標記化合物（３６）を得た。
【００９３】（参考例３７）（Ｌ）－Ｎ－〔１－（ベンジルオキシカルボニル）－ピペリジン－４－カルボニル〕ロイシン（化合物（３７））
Ｌ－ロイシンエチルエステル・塩酸塩５ｇ（２５．５mmol）のクロロホルム溶液（１００ml）に氷冷攪拌下トリエチルアミン２．５８ｇ（２５．５mmol）、Ｎ－（ベンジルオキシカルボニル）－ピペリジン－４－カルボン酸６．７ｇ（２５．５mmol）、１－エチル－３（３－ジメチルアミノプロピル）カルボジイミド・塩酸塩４．８８ｇ（２５．５mmol）を順次加え、室温に戻し一夜攪拌した。反応溶液を１Ｎ－塩酸、飽和炭酸水素ナトリウム溶液、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮し、Ｌ－Ｎ－〔１－（ベンジルオキシカルボニル）－ピペリジン－４－カルボニル〕ロイシンエチルエステル１０．１ｇ（収率９８％）を得た。
【００９４】得られた上記エステル体１０．１ｇのメタノール溶液に氷冷攪拌下水酸化ナトリウム１．０２ｇ（２５．５mmol）の水溶液（１０ml）を加えそのまま３時間攪拌した。反応溶液を減圧下濃縮し、得られた残留物を水に溶解し、エーテルで２回洗浄した。水層に濃塩酸を加え酸性（pH＝１）とした後酢酸エチルで２回抽出し、飽和食塩水で洗浄した。無水硫酸ナトリウムで乾燥後減圧下濃縮することにより標記化合物（３７）９．３ｇ（収率９６％）を油状物質として得た。
【００９５】NMR（δ，ＣＤＣｌ$_3$）：8.80-9.00(m,1H),7.32-7.38(m,5H),6.05-6.15(m,1H),5.14(s,2H),4.58-4.68(m,1H),4.16-4.26(m,2H),2.82-2.95(m,2H),2.37-2.48(m,1H),1.82-1.92(m,2H),1.56-1.75(m,5H),0.95-0.97(m,6H)
（参考例３８）（Ｌ）－Ｎ－（Ｎ－フェニルカルバモイル）ロイシン（化合物（３８））
（Ｌ）－ロイシンエチルエステル塩酸塩５ｇ（２５．５mmol）のクロロホルム溶液（２００ml）に氷冷攪拌下トリエチルアミン５．１６ｇ（５１mmol）を加え、次いでイソシアン酸フェニルエステル２．７６ml（２５．５mmol）のクロロホルム溶液を滴下した。一夜攪拌後、反応溶液を１Ｎ－塩酸、飽和炭酸水素ナトリウム溶液、飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮することにより、（Ｌ）－Ｎ－（Ｎ－フェニルカルバモイル）ロイシンエチルエステル５．８５ｇ（収率８２％）を得た。
【００９６】得られた上記化合物５．８５ｇのメタノール溶液（２００ml）に氷冷攪拌下水酸化ナトリウム１．８４８ｇ（４６mmol）の水溶液（１０ml）を加えそのまま３時間攪拌した。反応溶液を減圧下濃縮し、得られた残留物を水に溶解し、エーテルで２回洗浄した。水層に濃塩酸を加え酸性（pH＝１）とし、析出した結晶を濾取し水、冷エタノール、エーテルで順次洗浄し、乾燥することに標記化合物（３８）３．５５ｇ（収率６．７％）を得た。
【００９７】融点（℃）：１４３．８～１４５．８
NMR（δ，ＣＤ$_3$ＯＤ）：7.33(dd,J=8.5Hz,0.96Hz,2H),7.25(t,J=5.1Hz,2H),6.96(td,J=8.5Hz,1.2Hz,1H),4.37(dd,J=9.3Hz,5.1Hz,1H),1.51～1.89(m,3H),0.99(d,J=3.2Hz,3H),0.97(d,J=3.0Hz,3H)
（参考例３９）（Ｌ）－Ｎ－（４－メチルベンゼンスルホニル）ロイシン（化合物（３９））
参考例３９に準ずる方法でイソシアン酸フェニルエステルの代りに４－メチルベンゼンスルホニルクロリド４．８６ｇを用いて標記化合物（３９）６．２ｇを得た。
【００９８】融点（℃）：１１７．２～１２０
NMR（δ，ＣＤＣｌ$_3$）：7.73(d,J=8.3Hz,2H),7.28(d,J=8.3Hz,2H),5.07(d,J=9.7Hz,1H),3.86 ～3.99(m,1H),2.41(s,3H),1.70～1.85(m,1H),1.45 ～1.60(m,2H),0.89(d,J=6.6Hz,3H),0.82(d,J=6.5Hz,3H)
（参考例４０）（Ｌ）－Ｎ－メチル－Ｎ－（ベンジルオキシカルボニル）ロイシン（化合物（４０））
市販のＬ－Ｎ－メチルロイシン１ｇ（６．８８mmol）の１Ｎ－水酸化ナトリウム水溶液（１０ml）に氷冷攪拌下ベンジルオキシカルボニルクロリド０．９８２ml（６．８８mmol）のベンゼン溶液（１０ml）と１Ｎ－水酸化ナトリウム水溶液（１０ml）を同時に滴下した。室温に戻し一夜攪拌後反応溶液をエーテルで２回洗浄した。水層に濃塩酸を加え酸性（pH＝１）とした後酢酸エチルで２回抽出した。無水硫酸ナトリウムで乾燥後減圧下濃縮することにより標記化合物（４０）０．４６ｇを得た。
【００９９】NMR（δ，ＣＤＣｌ$_3$）：7.30-7.40(m,5H),5.10-5.23(m,2H),4.92(t,J=8.3Hz,2/3H),4.77(dd,J=10.5Hz,4.5Hz,1/3H),2.88(s,3H),1.45 ～1.82(m,3H),0.86～1.05(m,6H)
（実施例１）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－（１－ホルミル－２－ベンジルオキシ）エチルアミド（化合物（４１））
参考例１で合成した化合物（１）２．０１ｇ（７．８mmol）のクロロホルム懸濁液（２００ml）に氷冷攪拌下トリエチルアミン７８４mg（７．８mmol），Ｌ－Ｃｂｚ－Ｌｅｕ－ＯＨ・トルエン溶液２３ml（８．５mmol）および１－ヒドロキシベンズトリアゾール１．１８ｇ（７．８mmol）を順次加えた後ジシクロヘキシルカルボジイミド１．７６ｇ（８．５２５mmol）のクロロホルム溶液（５０ml）を滴下した。室温にて一夜攪拌した後不溶物を濾去し、濾液を１Ｎ－塩酸，飽和炭酸水素ナトリウム水溶液，飽和食塩水の順に洗浄した有機層を無水硫酸ナトリウムで乾燥後、濃縮して得られた残留物をシリカゲルカラムクロマトグラフィーで精製することによりＬ－

N－（ベンジルオキシカルボニル）－ロイシル－L－（O－ベンジル）－セリンエチルエステルを得た（2．74，75%）。得られたエステル体1．58g（3．4mmol）の無水テトラヒドロフラン溶液（50ml）に氷冷攪拌下、水素化ホウ素リチウム182mg（8．4mmol）を加え、次いでメタノール3mlを滴下した。さらに1時間攪拌後反応溶液に水10mlを滴下し、減圧下濃縮した。得られた残留物に1N－塩酸を加え酸性（pH=1）にした後塩化メチレンで2回抽出した。有機層を飽和炭酸水素ナトリウム溶液，飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥後濃縮して得られた残留物をベンゼン－酢酸エチルから再結晶し対応するアルコール0．965g（収率67%）を得た。得られたアルコール体900mg（2．1mmol）およびトリエチルアミン850mg（8．4mmol）の無水ジメチルスルホキシド溶液（10ml）に室温攪拌下三酸化イオウピリジンコレプレックス1．33g（8．4mmol）の無水ジメチルスルホキシド溶液（10ml）を滴下した。30分間攪拌後反応溶液を氷水に注ぎ酢酸エチルで3回抽出した。合わせた有機層を10%－クエン酸水溶液、水、飽和炭酸水素ナトリウム水溶液、飽和食塩水で順次洗浄し無水硫酸ナトリウムで乾燥後減圧下濃縮した。得られた残留物をシリカゲルカラムクロマトグラフィーで精製することにより標記化合物（41）0．425g（収率47%）を油状物質として得た。

【0100】NMR（δ，$CDCl_3$）：9.56(s,1H),7.25-7.36(m,10H),6.75-6.95(m,1H),5.20-5.22(m,1H),5.11(s,2H),4.55-4.59(m,1H),4.43-4.50(m,2H),4.25-4.35(m,1H),3.99-4.03(m,1H),3.66-3.70(m,1H),1.49-1.73(m,3H),0.92-0.95(m,6H)

Rf値：0．19（展開溶媒A，ヘキサン：酢酸エチル=1：1）

：0．14（展開溶媒B，塩化メチレン：アセトン=10：1）

（実施例2）L－N－ベンジルオキシカルボニルロイシン－（2R）－（1－ホルミル－2－ベンジルチオ）エチルアミド（化合物（42））

実施例1に準ずる方法で参考例1で合成した化合物（1）の代りに市販のL－S－ベンジル－システインエチルエステル塩酸塩2．2gを用いて標記化合物（42）0．14gを得た。

【0101】融点（℃）：116．8～122．1

NMR（δ，$CDCl_3$）：9.49(s,1H),7.28-7.34(m,10H),6.72-6.79(m,1H),5.11(s,2H),5.17-5.20(m,2H),4.48-4.57(m,1H),4.20-4.28(m,1H),3.71(s,2H),2.88(d,J=5.86Hz,2H),1.48-1.75(m,3H),0.95(d,J=5.97Hz,6H)

Rf値：0．35（展開溶媒A）

：0．25（展開溶媒B）

（実施例3）L－N－ベンジルオキシカルボニルロイシン－（2R）－〔1－ホルミル－2－（2－フェニルエチルチオ）〕エチルアミド（化合物（43））

実施例1に準ずる方法で参考例1で合成した化合物（1）の代りに参考例2で合成した化合物（2）3．3gを用いて標記化合物（43）0．57gを油状物質として得た。

【0102】NMR（δ，$CDCl_3$）：9.57(s,1H),7.18-7.36(m,10H),6.90-7.00(m,1H),5.15-5.20(m,1H),5.10(s,2H),4.48-4.55(m,1H),4.24-4.27(m,1H),2.77-2.96(m,6H),1.49-1.71(m,3H),0.92-0.95(m,6H)

Rf値：0．30（展開溶媒A）

：0．23（展開溶媒B）

（実施例4）L－N－ベンジルオキシカルボニルロイシン－（2R）－〔1－ホルミル－2－（3－フェニルプロピルチオ）〕エチルアミド（化合物（44））

実施例1に準ずる方法で参考例1で合成した化合物（1）の代りに参考例3で合成した化合物（3）3．47gを用いて標記化合物（44）0．79gを油状物質として得た。

【0103】NMR（δ，$CDCl_3$）：9.59(br s,1H),7.28-7.36(m,8H),7.15-7.21(m,2H),6.90-7.00(m,1H),5.11(s,2H),5.10-5.20(m,1H),4.50-4.58(m,1H),4.22-4.30(m,1H),2.95(br s,2H),2.69(t,J=7.33Hz,2H),2.53(t,J=7.32Hz,2H),1.84-1.94(m,2H),1.48-1.70(m,3H),0.94(d,J=6.73Hz,6H)

Rf値：0．31（展開溶媒A）

：0．26（展開溶媒B）

（実施例5）L－N－ベンジルオキシカルボニルロイシン－（2R）－〔1－ホルミル－2－（3－フェニルプロピルオキシ）〕エチルアミド（化合物（45））

実施例1に準ずる方法で参考例1で合成した化合物（1）の代りに参考例4で合成した化合物（4）1．13gを用いて標記化合物（45）0．315gを油状物質として得た。

【0104】NMR（δ，$CDCl_3$）：9.57(s,1H),7.25-7.36(m,8H),7.14-7.21(m,2H),6.77-6.93(m,1H),5.20-5.26(m,1H),5.05-5.14(m,2H),4.54-4.59(m,1H),4.27-4.32(m,1H),3.94-3.98(m,1H),3.61-3.65(m,1H),3.41(t,J=6.35Hz,2H),2.62(t,J=7.92Hz,2H),1.79-1.90(m,2H),1.51-1.79(m,3H),0.93-0.96(m,6H)

Rf値：0．18（展開溶媒A）

：0．16（展開溶媒B）

（実施例6）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－2－（チオフェン－3－イルメチル）オキシ〕エチルアミド（化合物（46））

実施例1に準ずる方法で参考例1で合成した化合物（1）の代りに参考例5で合成した化合物（5）1．20gを用いて標記化合物（46）0．33gを油状物質として得た。

【0105】NMR（δ，$CDCl_3$）：9.55(s,1H),

7.26-7.34(m,6H),7.18(s,1H),6.97-7.05(m,1H),6.70-6.93(m,1H),5.12(s,2H),5.10-5.20(m,1H),4.53-4.60(m,1H),4.49(s,2H),4.22-4.31(m,1H),3.97-4.05(m,1H),3.65-3.72(m,1H),1.50-1.75(m,3H),0.95(t,J=4.45Hz,6H)
Ｒｆ値：０．２１（展開溶媒Ａ）
：０．２４（展開溶媒Ｂ）
（実施例７）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－（１－ホルミル－２－ジフェニルメチルチオ）エチルアミド（化合物（４７））
実施例１に準ずる方法で参考例１で合成した化合物（１）の代りに参考例６で合成した化合物（６）１．１３ｇを用いて標記化合物（４７）０．１７ｇを油状物質として得た。
【０１０６】NMR（δ，ＣＤＣｌ$_3$）：9.44(s,1H),7.21-7.41(m,15H),6.72-6.85(m,1H),5.08-5.18(m,4H),4.46-4.51(m,1H),4.20-4.30(m,1H),2.75-2.92(m,2H),1.47-1.71(m,3H),0.93-0.95(m,6H)
Ｒｆ値：０．３２（展開溶媒Ａ）
：０．２５（展開溶媒Ｂ）
（実施例８）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－（１－ホルミル－２－シクロヘキシルメチルチオ）エチルアミド（化合物（４８））
実施例１に準ずる方法で合成した化合物（１）の代りに参考例７で合成した化合物（７）２．５３ｇを用いて標記化合物（４８）０．７４ｇを油状物質として得た。
【０１０７】NMR（δ，ＣＤＣｌ$_3$）：9.61(s,1H),7.35(s,5H),6.89-6.93(m,1H),5.12(s,2H),5.10-5.20(s,1H),4.51-4.57(m,1H),4.22-4.30(m,1H),2.92-2.96(m,2H),2.42(d,J=6.84Hz,2H),1.28-1.82(m,10H),1.11-1.26(m,4H),0.95(d,J=6.02Hz,6H)
Ｒｆ値：０．３８（展開溶媒Ａ）
：０．２８（展開溶媒Ｂ）
（実施例９）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－（１－ホルミル－２－シクロペンチルチオ）エチルアミド（化合物（４９））
実施例１に準ずる方法で参考例１で合成した化合物（１）の代りに参考例８で合成した化合物（８）２．０ｇを用いて標記化合物（４９）０．２９ｇを油状物質として得た。
【０１０８】NMR（δ，ＣＤＣｌ$_3$）：9.62(s,1H),7.35(s,5H),6.89-6.92(m,1H),5.12(s,2H),5.10-5.20(m,1H),4.55-4.60(m,1H),4.32-4.41(m,1H),2.90-3.12(m,3H),1.95-2.05(m,3H),1.46-1.72(m,8H),0.95(d,J=5.26Hz,6H)
Ｒｆ値：０．３７（展開溶媒Ａ）
：０．３２（展開溶媒Ｂ）
（実施例１０）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（チオフェン－２－イルメチル）チオ〕エチルアミド（化合物（５０））
実施例１に準ずる方法で参考例１で合成した化合物（１）の代りに参考例９で合成した化合物（９）０．９８ｇを用いて標記化合物（５０）０．２２ｇを油状物質として得た。
【０１０９】NMR（δ，ＣＤＣｌ$_3$）：9.50(s,1H),7.34(s,5H),7.21-7.23(m,1H),6.89-6.96(m,2H),6.79-6.83(m,1H),5.12(s,2H),5.11-5.17(m,1H),4.48-4.53(m,1H),4.21-4.30(m,1H),3.92(s,2H),2.94(d,J=5.76,2H),1.49-1.72(m,3H),0.95(d,J=6.08Hz,6H)
Ｒｆ値：０．２８（展開溶媒Ａ）
：０．１８（展開溶媒Ｂ）
（実施例１１）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（チオフェン－３－イルメチル）チオ〕エチルアミド（化合物（５１））
実施例１に準ずる方法で参考例１で合成した化合物（１）の代りに参考例１０で合成した化合物（１０）２．５ｇを用いて標記化合物（５１）１．４９ｇを油状物質として得た。
【０１１０】NMR（δ，ＣＤＣｌ$_3$）：9.49(s,1H),7.26-7.34(m,6H),7.16(s,1H),7.05(d,J=4.93,1H),6.79-6.91(m,1H),5.14-5.18(m,1H),5.12(s,2H),4.48-4.52(m,1H),4.20-4.30(m,1H),3.73(s,2H),2.86(br s,2H),1.49-1.71(m,3H),0.95(d,J=5.96Hz,6H)
Ｒｆ値：０．３３（展開溶媒Ａ）
：０．２２（展開溶媒Ｂ）
（実施例１２）Ｌ－Ｎ－〔１－（ベンジルオキシカルボニル）－ピペリジン－４－カルボニル〕ロイシン－（２Ｒ）－〔１－ホルミル－２－ベンジルチオ）エチルアミド（化合物（５２））
実施例１に準ずる方法でＮ－（ベンジルオキシカルボニル）ロイシンの代りに参考例３７で合成した化合物（３８）と参考例１で合成した化合物（１）の代りに市販のＬ－Ｓ－ベンジル－システインエチルエステル塩酸塩０．９８ｇを用いて標記化合物（５２）０．３９ｇを油状物質として得た。
【０１１１】NMR（δ，ＣＤＣｌ$_3$）：9.46(s,1H),7.24-7.36(m,10H),6.25-6.40(m,1H),5.11(s,2H),4.56-4.59(m,1H),4.42-4.47(m,1H),4.10-4.25(m,2H),3.70(d,J=3.27Hz,2H),2.74-2.91(m,4H),2.25-2.33(m,1H),1.52-1.82(m,8H),0.93(t,J=5.58Hz,6H)
Ｒｆ値：０．０４（展開溶媒Ａ）
：０．０５（展開溶媒Ｂ）
（実施例１３）Ｌ－Ｎ－（ベンジルオキシカルボニル）ロイシン－（２Ｒ）－〔１－ホルミル－２－（ナフタレン－１－イルメチルチオ）〕エチルアミド（化合物（５３））
参考例１１で合成した化合物（１１）１．２５ｇ（３．９８mmol）とＬ－Ｎ－（ベンジルオキシカルボニル）ロイシン　Ｎ－ヒドロキシスクシンイミドエステル１．４

5g（3．98mmol）のクロロホルム溶液に氷冷攪拌下トリエチルアミン0．81g（3．98mmol）を滴下しさらに一夜攪拌した。反応溶液を1N－塩酸水溶液，飽和炭酸水素ナトリウム水溶液さらに水で洗浄し、無水硫酸ナトリウムで乾燥し減圧下溶媒留去し得られた残留物をシリカゲルカラムクロマトグラフィーにて精製しエステル体であるL－N－（ベンジルオキシカルボニル）－ロイシル－（L）－S－（ナフタレン－1－イル－メチル）システインエチルエステル0．9g（42%）を得た。得られたエステル体0．9g（1．68mmol）の無水テトラヒドロフラン溶液に水素化ホウ素リチウム0．073g（3．35mmol）を加え、氷冷下メタノールを滴下し3時間攪拌した反応溶液に水を滴下し減圧下溶媒留去した。得られた残留物の水溶液を1N－塩酸水溶液で酸性とし酢酸エチルで抽出し水洗後無水硫酸ナトリウムで乾燥し減圧下溶媒留去し得られた残留物をシリカゲルカラムクロマトグラフィーで精製してアルコール体0．577gを得た（収率69%）。

【0112】アルコール体0．55g（1．11mmol）とトリエチルアミン0．45g（4．44mmol）の無水ジメチルスルホキシド溶液に室温攪拌下に三酸化イオウ－ピリジンコンプレックス0．708g（4．44mmol）ジメチルスルホキシド溶液を滴下し室温で1時間攪拌した。反応溶液を氷水に注ぎ、酢酸エチルで3回抽出し、10%クエン酸水溶液，飽和食塩水，飽和炭酸水素ナトリウム水溶液及び飽和食塩水の順で洗浄し無水硫酸ナトリウムで乾燥し減圧下溶媒留去し得られた残留物をシリカゲルカラムクロマトグラフィーで精製し標記化合物（53）0．26g（収率47%）を得た。

【0113】融点（℃）：115．0～126．1（分解）

NMR（δ，$CDCl_3$）：9.46(s,1H),8.06(d,J=7.92Hz,1H),7.86(d,J=9.23,1H),7.76-7.80(m,2H),7.31-7.58(m,8H),6.75-6.90(m,1H),5.08(d,J=3.78Hz,2H),4.98-5.05(m,1H),4.48-4.58(m,1H),4.17-4.27(m,1H),4.17(s,2H),2.90-2.93(m,2H),1.35-1.72(m,3H),0.91-0.93(m,6H)

Rf値：0．28（展開溶媒A）

：0．22（展開溶媒B）

（実施例14）L－N－ベンジルオキシカルボニルロイシン－（2R）－〔1－ホルミル－2（ナフタレン－2－イルメチル）チオ〕エチルアミド（化合物（54））

実施例13に準ずる方法で、参考例11で合成した化合物（11）の代りに参考例12で合成した化合物（12）1．26gを用いて標記化合物（54）0．1gを油状物質として得た。

【0114】NMR（δ，$CDCl_3$）：9.48(d,J=5.10Hz,1H),7.71-7.83(m,3H),7.32-7.49(m,9H),6.80-6.82(m,1H),5.11(d,J=3.36Hz,2H),5.07-5.18(m,1H),5.50-5.57(m,1H),4.22-4.30(m,1H),3.87(s,2H),2.87(d,J=5.01Hz,2H),1.45-1.80(m,3H),0.93(d,J=6.36Hz,6H)

Rf値：0．29（展開溶媒A）

：0．22（展開溶媒B）

（実施例15）L－N－ベンジルオキシカルボニルロイシン－（2R）－〔1－ホルミル－2－（2－クロロベンジル）チオ〕エチルアミド（化合物（55））

実施例13に準ずる方法で参考例11で合成した化合物（11）の代りに参考例13で合成した化合物（13）1．24gを用いて標記化合物（55）0．57gを得た。

【0115】融点（℃）：128．6～131．9

NMR（δ，$CDCl_3$）：9.55(s,1H),7.20-7.40(m,9H),6.83-6.91(m,1H),5.10-5.20(br s,3H),4.52-4.60(m,1H),4.20-4.30(m,1H),3.84(s,2H),2.93(br s,2H),1.49-1.73(m,4H),0.95(d,J=4.29Hz,6H)

Rf値：0．31（展開溶媒A）

：0．24（展開溶媒B）

（実施例16）L－N－メチル－N－（ベンジルオキシカルボニル）ロイシン－（2R）－〔1－ホルミル－2－（4－クロロベンジルチオ）〕エチルアミド（化合物（56））

参考例40で合成した化合物（40）0．9g（3．22mmol），トリエチルアミン0．326g（3．22mmol）1－ヒドロキシベンズトリアゾール0．443g（3．22mmol）および参考例16で合成した化合物（17）0．748g（3．22mmol）のクロロホルム溶液（100ml）に塩－氷浴で冷却攪拌下ジシクロヘキシルカルボジイミド0．664g（3．22mmol）のクロロホルム溶液を滴下した。さらに一夜攪拌した。不溶物を濾去し、濾液を1N－塩酸，飽和$NaHCO_3$溶液，飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮した。得られた残留物をシリカゲルカラムクロマトグラフィーで精製することによりL－N－メチル－N－（ベンジルオキシカルボニル）ロイシン－（2R）－〔1－ヒドロキシメチル－2－（4－クロロフェニル）〕エチルアミド1．2g（収率75%）を得た。

【0116】得られた上記化合物0．89g（1．8mmol）およびトリエチルアミン0．13g（7．22mmol）の無水ジメチルスルホキシド溶液（10ml）に室温攪拌下三酸化イオウ－ピリジンコンプレックス1．14g（7．22mmol）の無水ジメチルスルホキシド溶液（10ml）を滴下、さらに30分間攪拌した。反応溶液を氷水に注ぎ酢酸エチルで3回抽出した。合わせた有機層を10%－クエン酸水溶液，水，飽和炭酸水素ナトリウム水溶液，飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮した。得られた残留物をシリカゲルカラムクロマトグラフィーで精製することにより標記化合物（56）0．52gを油状物質として得た。

【0117】NMR（δ，$CDCl_3$）：9.50(s,1H),7.15-7.40(m,9H),6.80-6.95(m,1H),5.10-5.30(m,2H),4.

60-4.90(m,1H),4.40-4.55(m,1H),3.60-3.71(m,2H),2.85(s,3H),2.60-2.85(m,2H),1.60-1.80(m,2H),1.42-1.60(m,1H),0.80-1.05(m,6H)
Rf値：０．４２（展開溶媒A）
：０．３０（展開溶媒B）

（実施例１７）L－N－（N－フェニルカルバモイル）ロイシン－（２R）－〔１－ホルミル－２－（４－クロロベンジルチオ）〕エチルアミド（化合物（５７））

実施例１６に準ずる方法で参考例４０で合成した化合物（４０）の代りに参考例３８で合成した化合物（３８）１gを用いて標記化合物（５７）０．３４gを非結晶質として得た。

【０１１８】NMR（δ，CDCl$_3$）：9.40(s,1H),7.97(bs,1H),7.05 〜7.45(m,9H),6.63(bs,1H),4.50 〜4.60(m,1H),4.30 〜4.40(m,1H),3.60 〜3.75(m,2H),3.10 〜3.30(m,2H),1.45 〜1.85(m,3H),0.85 〜1.10(m,6H)
Rf値：０．２０（展開溶媒A）
：０．１０（展開溶媒B）

（実施例１８）L－N－（４－メチルベンゼンスルホニル）ロイシン－（２R）－〔１－ホルミル－２－（４－クロロベンジルチオ）〕エチルアミド（化合物（５８））

実施例１６に準ずる方法で参考例４０で合成した化合物（４０）の代りに参考例３９で合成した化合物（３９）１gを用いて標記化合物（５８）０．５４gを非結晶質として得た。

【０１１９】NMR（δ，CDCl$_3$）：9.37(s,1H),7.73(d,J=8.2Hz,2H),7.20-7.35(m,6H),6.61(d,J=8.4Hz,1H),4.99(d,J=5.8Hz,1H),4.29-4.45(m,2H),3.63(s,2H),2.70〜2.90(m,2H),2.40(s,3H),1.40〜1.70(m,3H),0.90〜1.10(m,6H)
Rf値：０．３３（展開溶媒A）
：０．２５（展開溶媒B）

（実施例１９）L－N－（ベンジルオキシカルボニル）フェニルアラニン－（２R）－〔１－ホルミル－２－（４－クロロベンジルチオ）〕エチルアミド（化合物（５９））

実施例１６に準ずる方法で参考例４０で合成した化合物（４０）の代りに市販の（L）－N－（ベンジルオキシカルボニル）フェニルアラニン１gを用いて標記化合物（５９）０．４gを得た。

【０１２０】融点（℃）：１２９．４〜１３３．４
NMR（δ，CDCl$_3$）：9.38(s,1H),7.10 〜7.41(m,14H),6.30〜6.40(m,1H),5.20 〜5.30(m,1H),5.09(s,2H),4.35〜4.51(m,2H),3.35 〜3.45(m,2H),3.00〜3.20(m,2H),2.70 〜2.80(m,2H)
Rf値：０．３６（展開溶媒A）
：０．２４（展開溶媒B）

（実施例２０）（L）－N－（ベンジルオキシカルボニル）－バリン－（２R）－〔１－ホルミル－２－（４－クロロベンジルチオ）〕エチルアミド（化合物（６０））

実施例１６に準ずる方法で参考例４０で合成した化合物（４０）の代りに市販のL－N－（ベンジルオキシカルボニル）バリン１gを用いて標記化合物（６０）０．１４gを得た。

【０１２１】融点（℃）：１２６．２〜１２８．７
NMR（δ，CDCl$_3$）：9.52(s,1H),7.20 〜7.45(m,9H),6.60 〜6.75(m,1H),5.25 〜5.35(m,1H),5.11(s,2H),4.50〜4.61(m,1H),4.00 〜4.15(m,1H),3.68(s,2H),2.75〜2.90(m,2H),2.10 〜2.25(m,1H),0.90 〜1.05(m,6H)
Rf値：０．３６（展開溶媒A）
：０．２１（展開溶媒B）

（実施例２１）L－N－（ベンジルオキシカルボニル）ロイシン－（２R）－〔１－ホルミル－２－（４－クロロベンジル）チオ〕エチルアミド（化合物（６１））

参考例１６で合成した化合物（１７）４g（１７．２６mmol）およびトリエチルアミン１．７４g（１７．２６mmol）のクロロホルム溶液（２００ml）に氷冷攪拌下L－N－（ベンジルオキシカルボニル）ロイシン N－ヒドロキシスクシンイミドエステル６．２５g（１７．２６mmol）を少量ずつ加え、室温に戻した後一夜攪拌した。反応溶液を１N－塩酸，飽和炭酸水素ナトリウム溶液（３回），飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮し、アルコール体である（L）－N－（ベンジルオキシカルボニル）ロイシン－（２R）－〔１－ヒドロキシメチル－２－（４－クロロベンジルチオ）〕エチルアミド７．８g（９４%）を得た。得られた上記アルコール体７．８g（１６．２８mmol）およびトリエチルアミン６．５７g（６５mmol）の無水ジメチルスルホキシド溶液（１００ml）に室温攪拌下三酸化イオウピリジンコンプレックス１０．３４g（６５mmol）の無水ジメチルスルホキシド溶液（３０ml）を滴下した。３０分間攪拌後、反応溶液を氷水に注ぎ酢酸エチルで３回抽出した。合わせた有機層を１０%－クエン酸水溶液水，飽和炭酸水素ナトリウム溶液，飽和食塩水で順次洗浄し、無水硫酸ナトリウムで乾燥後減圧下濃縮した。得られた残留物をシリカゲルカラムクロマトグラフィーで精製し標記化合物（６１）２．４gを得た。

【０１２２】融点（℃）：１１６．０〜１３０．７（分解）
NMR（δ，CDCl$_3$）：9.52(d,J=4.88Hz,1H),7.22-7.33(m,10H),6.83-6.91(m,1H),5.11(d,J=2.33Hz,3H),4.50-4.59(m,1H),4.23-4.30(m,1H),3.67(s,2H),2.85(d,J=4.99Hz,2H),1.49-1.72(m,3H),0.94-0.96(m,6H)
Rf値：０．２５（展開溶媒A）
：０．１９（展開溶媒B）

（実施例２２）L－N－ベンジルオキシカルボニルロイシン－（２R）－〔１－ホルミル－２－（３－クロロベ

ンジル）チオ〕エチルアミド（化合物（６２））
実施例２１に準ずる方法で参考例１６で合成された化合物（１６）の代りに参考例１５で合成した化合物（１５）３．０ｇを用いて標記化合物（６２）０．６８ｇを得た。

【０１２３】融点（℃）：９７．６～１０３．３
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.53(s,1H),7.16-7.34(m,9H),6.84-6.90(m,1H),5.11(s,2H),5.10-5.17(m,1H),4.50-4.60(m,1H),4.20-4.30(m,1H),3.68(s,2H),2.80-2.93(m,2H),1.48-1.76(m,3H),0.94-0.97(m,6H)
Ｒｆ値：０．２５（展開溶媒Ａ）
：０．１８（展開溶媒Ｂ）

（実施例２３）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（２－フルオロベンジル）チオ〕エチルアミド（化合物（６３））
実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例１４で合成した化合物（１４）８．７ｇを用いて標記化合物（６３）２．７５ｇを得た。

【０１２４】融点（℃）：１１０．１～１１８．３
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.54(s,1H),7.08-7.34(m,7H),7.02-7.12(m,2H),6.83(br s,1H),5.11(s,3H),4.50-4.60(m,1H),4.20-4.30(m,1H),3.75(d,J=2.93Hz,2H),2.93(d,J=5.48Hz,2H),1.50-1.75(m,3H),0.95(d,J=6.18Hz,6H)
Ｒｆ値：０．３０（展開溶媒Ａ）
：０．２２（展開溶媒Ｂ）

（実施例２４）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（３－フルオロベンジル）チオ〕エチルアミド（化合物（６４））
実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例１７で合成した化合物（１７）６．５ｇを用いて標記化合物（６４）０．３７ｇを得た。

【０１２５】融点（℃）：１１１．８～１１６．６
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.53(s,1H),7.24-7.34(m,6H),7.06(t,J=8.19Hz,1H),6.95(t,J=8.96Hz,1H),6.81-6.87(m,1H),5.11(s,3H),4.50-4.59(m,1H),4.21-4.30(m,1H),3.70(s,7H),2.87(d,J=5.37Hz,2H),1.45-1.73(m,3H),0.94-0.97(m,6H)
Ｒｆ値：０．２３（展開溶媒Ａ）
：０．１９（展開溶媒Ｂ）

（実施例２５）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（４－フルオロベンジル）チオ〕エチルアミド（化合物（６５））
実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例１８で合成した化合物（１８）６．４６ｇを用いて標記化合物（６５）０．８ｇを得た。

【０１２６】融点（℃）：７１．２～７６．３
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.52(d,J=5.37Hz,1H),7.25-7.34(m,7H),6.95-7.07(m,2H),6.82-6.90(m,1H),5.11-5.20(m,3H),4.50-4.60(m,1H),4.20-4.30(m,1H),3.69(s,2H),2.80-2.90(m,2H),1.49-1.73(m,3H),0.95(d,J=4.12Hz,6H)
Ｒｆ値：０．２５（展開溶媒Ａ）
：０．２０（展開溶媒Ｂ）

（実施例２６）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（２－メトキシベンジル）チオ〕エチルアミド（化合物（６６））
実施例２１に準ずる方法で参考例１７で合成した化合物（１７）の代りに参考例１９で合成した化合物（１９）５．０ｇを用いて標記化合物（６６）０．８８ｇを得た。

【０１２７】融点（℃）：１１０．８～１２０．２
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.51(s,1H),7.22-7.34(m,7H),6.86-6.97(m,2H),6.80-6.85(m,1H),5.15-5.25(m,1H),5.11(s,2H),4.51-4.59(m,1H),4.22-4.28(m,1H),3.83(s,3H),3.85(d,J=5.42Hz,1H),3.74(d,J=5.7Hz,1H),2.91(d,J=5.86Hz,2H),1.42-1.74(m,3H),0.93-0.96(m,6H)
Ｒｆ値：０．２７（展開溶媒Ａ）
：０．２０（展開溶媒Ｂ）

（実施例２７）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（３－メトキシベンジル）チオ〕エチルアミド（化合物（６７））
実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２０で合成した化合物（２０）３．４１ｇを用いて標記化合物（６７）０．７１ｇを得た。

【０１２８】融点（℃）：１１３．８～１１７．８
ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.50(s,1H),7.20-7.34(m,6H),6.76-6.90(m,4H),4.49-4.53(m,1H),4.23-4.30(m,1H),3.80(s,3H),3.68(s,2H),2.88(d,J=5.75Hz,2H),1.50-1.75(m,3H),0.95(d,J=5.97Hz,6H)
Ｒｆ値：０．２５（展開溶媒Ａ）
：０．１９（展開溶媒Ｂ）

（実施例２８）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（４－メトキシベンジル）チオ〕エチルアミド（化合物（６８））
実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２１で合成した化合物（２１）４．５４ｇを用いて標記化合物（６８）０．１３ｇを油状物質として得た。

【０１２９】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.45(br s,1H),7.30-7.35(m,5H),7.22(d,J=8.57Hz,2H),6.85(d,J=7.54Hz,2H),6.76-6.89(m,1H),5.11(s,2H),5.08-5.18(m,1H),4.45-4.52(m,1H),4.20-4.30(m,1H),3.79(s,3H),2.78-2.89(m,2H),1.46-1.85(m,3H),0.94(d,J=5.86Hz,6H)
Ｒｆ値：０．１９（展開溶媒Ａ）
：０．２６（展開溶媒Ｂ）

（実施例２９）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－３－ニトロベンジル）チオ〕エチルアミド（化合物（６９））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２２で合成した化合物（２２）４．１８ｇを用いて標記化合物（６９）０．３７ｇを得た。

【０１３０】融点（℃）：７２．９～１０４．９（分解）

ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.56(d,J=6.95Hz,1H),8.21(s,1H),8.13(dd,J=2.44Hz,7.22Hz,1H),7.65(d,J=7.43Hz),7.45-7.52(m,1H),7.33(d,J=4.1Hz,5H),6.91-7.07(m,1H),5.20(d,J=7.70Hz,1H),5.11(d,J=5.48Hz,2H),4.53-4.59(m,1H),4.20-4.35(m,1H),3.80(s,2H),2.80-2.95(m,2H),1.51-1.80(m,3H),0.95(d,J=5.68Hz,6H)

Ｒｆ値：０．１７（展開溶媒Ａ）

：０．１７（展開溶媒Ｂ）

（実施例３０）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｒ）－〔１－ホルミル－２－（４－ニトロベンジル）チオ〕エチルアミド（化合物（７０））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２３で合成した化合物（２３）２．１７ｇを用いて標記化合物（７０）０．１ｇを油状物質として得た。

【０１３１】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.56(s,1H),8.15-8.20(m,2H),7.47-7.51(m,2H),7.30-7.34(m,5H),6.84-7.00(m,1H),5.05-5.15(m,3H),4.53-4.60(m,1H),4.20-4.30(m,1H),3.79(s,2H),2.87(d,J=5.26Hz,2H),1.49-1.75(m,3H),0.94-0.97(m,6H)

Ｒｆ値：０．１５（展開溶媒Ａ）

：０．１５（展開溶媒Ｂ）

（実施例３１）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－〔１－ホルミル－３－フェニルオキシ）プロピルアミド（化合物（７１））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２５で合成した化合物（２４）０．５２ｇを用いて標記化合物（７１）０．５２ｇを油状物質として得た。

【０１３２】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.64(s,1H),7.24-7.33(m,8H),6.82-6.98(m,3H),4.95-5.15(m,3H),4.55-4.59(m,1H),4.20-4.30(m,1H),3.95-4.10(m,2H),2.27-2.53(m,2H),1.45-1.72(m,3H),0.92(t,J=6.24Hz,6H)

Ｒｆ値：０．２６（展開溶媒Ａ）

：０．１９（展開溶媒Ｂ）

（実施例３２）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－〔１－ホルミル－３－フェニルチオ）プロピルアミド（化合物（７２））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２５で合成した化合物（２５）０．８７ｇを用いて標記化合物（７２）０．４２ｇを油状物質として得た。

【０１３３】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.52(d,J=6.24Hz,1H),7.12-7.38(m,10H),6.71-6.86(m,1H),5.14-5.16(d,J=6.95Hz,1H),5.10(s,2H),4.51-4.59(m,1H),4.20-4.25(m,1H),2.91-2.96(m,2H),2.25-2.35(m,1H),1.85-2.00(m,1H),1.48-1.72(m,3H),0.92-0.96(m,6H)

Ｒｆ値：０．３１（展開溶媒Ａ）

：０．２４（展開溶媒Ｂ）

（実施例３３）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－〔１－ホルミル－２－（２－クロロベンジル）オキシ〕エチルアミド（化合物（７３））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２６で合成した化合物（２６）０．５５ｇを用いて標記化合物（７３）０．５０ｇを油状物質として得た。

【０１３４】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.61(s,1H),7.23-7.36(m,9H),6.80-6.93(m,1H),5.09-5.17(m,3H),4.55-4.63(m,3H),4.25-4.35(m,1H),4.08-4.16(m,1H),3.75-3.79(m,1H),1.49-1.71(m,3H),0.92-0.96(m,6H)

Ｒｆ値：０．３１（展開溶媒Ａ）

：０．２４（展開溶媒Ｂ）

（実施例３４）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－〔１－ホルミル－３－（２－フルオロフェニル）オキシ〕プロピルアミド（化合物（７４））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２７で合成した化合物（２７）０．６９ｇを用いて標記化合物（７４）０．６６ｇを油状物質として得た。

【０１３５】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.65(s,1H),7.28-7.37(m,5H),7.02-7.10(m,3H),6.88-6.95(m,2H),5.10-5.22(m,1H),5.06(s,2H),4.57-4.61(m,1H),4.22-4.30(m,1H),4.05-4.13(m,2H),2.32-2.50(m,2H),1.50-1.72(m,3H),0.91-0.95(m,6H)

Ｒｆ値：０．２６（展開溶媒Ａ）

：０．１９（展開溶媒Ｂ）

（実施例３５）Ｌ－Ｎ－ベンジルオキシカルボニルロイシン－（２Ｓ）－〔１－ホルミル－３－（３－フルオロフェニル）オキシ〕プロピルアミド（化合物（７５））

実施例２１に準ずる方法で参考例１６で合成した化合物（１６）の代りに参考例２８で合成した化合物（２８）０．２７ｇを用いて標記化合物（７５）０．０６ｇを油状物質として得た。

【０１３６】ＮＭＲ（δ，ＣＤＣｌ$_3$）：9.64(s,1H),7.30-7.35(m,5H),7.20(q,J=8.25Hz,1H),6.81-6.88(m,1H),6.54-6.70(m,3H),5.05-5.12(m,3H),4.56-4.63(m,1H),4.17-4.27(m,1H),3.96-4.04(m,2H),2.27-2.54(m,2H),1.45-1.75(m,3H),0.88-0.95(m,6H)

Ｒｆ値：０．２５（展開溶媒Ａ）

：０．１９（展開溶媒Ｂ）

（実施例３６）Ｌ－Ｎ－ベンジルオキシカルボニルロイ

シン－（2S）－〔1－ホルミル－3－（2－クロロフェニル）オキシ〕プロピルアミド（化合物（76））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例29で合成した化合物（29）1．05gを用いて標記化合物（76）0．41gを得た。
【0137】融点（℃）：107．1～111．3
NMR（δ，CDCl$_3$）：9.70(s,1H),7.33-7.39(m,5H),7.18-7.23(m,2H),7.06-7.09(m,1H),6.85-6.94(m,2H),5.17-5.19(m,1H),5.07(s,2H),4.60-4.64(m,1H),4.26-4.29(m,1H),4.06-4.10(m,2H),2.42-2.46(m,2H),1.45-1.75(m,3H),0.90-0.98(m,6H)
Rf値：0．27（展開溶媒A）
：0．20（展開溶媒B）
（実施例37）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3－（3－クロロフェニル）オキシ〕プロピルアミド（化合物（77））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例30で合成した化合物（30）1．07gを用いて標記化合物（77）0．42gを油状物質として得た。
【0138】NMR（δ，CDCl$_3$）：9.63(s,1H),7.28-7.35(m,6H),7.17(t,J=8.19Hz,1H),6.92-6.95(m,1H),6.85(s,1H),6.72(d,J=8.31Hz,1H),5.03-5.18(m,3H),4.56-4.59(m,1H),4.16-4.22(m,1H),3.93-4.03(m,2H),2.25-2.53(m,2H),1.47-1.70(m,3H),0.91-0.95(m,6H)
Rf値：0．28（展開溶媒A）
：0．27（展開溶媒B）
（実施例38）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3－ベンジルチオ）プロピルアミド（化合物（78））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例31で合成した化合物（31）1．9gを用いて標記化合物（78）0．8gを得た。
【0139】融点（℃）：72．8～81．8
NMR（δ，CDCl$_3$）：9.49(d,J=5.76Hz,1H),7.24-7.33(m,10H),6.67-6.69(m,1H),5.14-5.18(m,1H),5.10(s,2H),4.55-4.64(m,1H),4.15-4.21(m,1H),3.66(s,2H),2.39-2.43(m,2H),2.11-2.20(m,1H),1.82-1.90(m,1H),1.47-1.69(m,3H),0.92-0.95(m,6H)
Rf値：0．52（展開溶媒A）
：0．25（展開溶媒B）
（実施例39）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3－（2－フルオロベンジル）チオ〕プロピルアミド（化合物（79））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例32で合成した化合物（32）1．6gを用いて標記化合物（79）1．3gを得た。
【0140】融点（℃）：99．6～101．0
NMR（δ，CDCl$_3$）：9.54(s,1H),7.19-7.37(m,7H),6.67-6.69(m,1H),5.11(s,2H),5.10-5.15(m,1H),4.50-4.54(m,1H),4.18-4.23(m,1H),3.70(s,2H),2.45-2.48(m,2H),2.18-2.30(m,2H),1.86-1.97(m,2H),1.48-1.72(m,3H),0.95(d,J=6.24Hz,6H)
Rf値：0．51（展開溶媒A）
：0．24（展開溶媒B）
（実施例40）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3（2－クロロベンジル）チオ〕プロピルアミド（化合物（80））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例33で合成した化合物（33）1．2gを用いて標記化合物（80）0．72gを油状物質として得た。
【0141】NMR（δ，CDCl$_3$）：9.53(d,J=6.46Hz,1H),7.30-7.38(m,7H),7.16-7.25(m,2H),6.73-6.75(m,1H),5.20(d,J=7.81Hz,1H),5.10(s,2H),4.47-4.53(m,1H),4.18-4.24(m,1H),3.80(s,2H),2.47-2.52(m,2H),2.16-2.24(m,1H),1.88-1.94(m,1H),1.48-1.68(m,3H),0.92-0.94(m,6H)
Rf値：0．29（展開溶媒A）
：0．26（展開溶媒B）
（実施例41）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3（2－フルオロフェニル）チオ〕プロピルアミド（化合物（81））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例34で合成した化合物（34）1．35gを用いて標記化合物（81）0．96gを油状物質として得た。
【0142】NMR（δ，CDCl$_3$）：9.54(d,J=6.73,1H),7.31-7.40(m,5H),7.22-7.29(m,2H),7.03-7.12(m,1H),5.17(d,J=7.81Hz,1H),5.11(s,1H),4.55-4.60(m,1H),4.20-4.30(m,1H),2.89-2.94(m,2H),2.10-2.20(m,1H),1.84-1.95(m,1H),1.49-1.73(m,3H),0.93-0.96(m,6H)
Rf値：0．42（展開溶媒A）
：0．40（展開溶媒B）
（実施例42）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3（2－クロロフェニル）チオ〕プロピルアミド（化合物（82））
実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例35で合成した化合物（35）1．25gを用いて標記化合物（82）0．58gを得た。
【0143】融点（℃）：109．5～149．0（分解）
NMR（δ，CDCl$_3$）：9.54(s,1H),7.12-7.40(m,9H),6.62-6.85(m,1H),5.09-5.15(m,3H),4.54-4.60(m,1H),4.21-4.25(m,1H),2.94-3.00(m,2H),2.27-3.40(m,1H),1.90-2.02(m,1H),1.49-1.71(m,3H),0.93-0.95(m,6H)
Rf値：0．27（展開溶媒A）
：0．27（展開溶媒B）

（実施例43）L－N－ベンジルオキシカルボニルロイシン－（2S）－〔1－ホルミル－3（4－クロロフェニル）チオ〕プロピルアミド（化合物（83））

実施例21に準ずる方法で参考例16で合成した化合物（16）の代りに参考例36で合成した化合物（36）1．58gを用いて標記化合物（83）0．71gを油状物質として得た。

【0144】NMR（δ，$CDCl_3$）：9.52(d,J=7.21Hz,1H),7.32(s,5H),7.25(s,4H),6.72-6.90(m,1H),5.14-5.17(m,1H),5.10(d,J=4.88Hz,2H),4.53-4.60(m,1H),4.15-4.25(m,1H),2.88-2.93(m,2H),2.20-2.35(m,1H),1.82-1.98(m,1H),1.49-1.68(m,3H),0.93-0.98(m,6H)

Rf値：0．30（展開溶媒A）

：0．30（展開溶媒B）

（試験例1）カルパイン阻害活性の測定

カルパインは、日本白色種ウサギ骨格筋より、TsujiとImahori（J．Biochem．90，233－240（1981））の方法に従って部分精製し、実験に使用した。

【0145】抗カルパイン活性の測定はYoshimura（J．Biol．Chem．258，8883－8889（1983））等の方法に従って行った。即ち、4%カゼイン溶液0．05ml，50mMシステイン溶液0．05ml，カルパイン溶液0．05ml，精製水0．025ml被験薬溶液（10%ジメチルスルホオキシド溶液）0．025ml及び200mMイミダゾール塩酸緩衝液（pH7．5）0．25mlを含む混合液を30℃で3分間加温した。その後、50mM塩化カルシウム溶液0．05mlを加えて反応を開始した。30℃，30分間反応した後、5%トリクロロ酢酸0．5mlを加えて反応を停止した。カルパインにより加水分解されたカゼインのトリクロロ酢酸可溶画分中のタンパク量をRossとSchatz（Anal．Biochem．54，304－306（1973））の方法に従って測定し、吸光度（a）を求めた。同時に被験薬溶液の代わりに10%ジメチルスルホオキシド溶液のみを用いた盲検の吸光度（b）を測定した。カルパイン阻害率は、次式〔（b－a）／b〕×100により計算し、50%阻害に必要な量〔IC_{50}〕をプロビット法より算出した。各実施例で製造した化合物を被験薬とし、測定結果を表1に示す。

【0146】

【表1】

化合物	カルパイン 阻害活性IC$_{50}$（μM）	化合物	カルパイン 阻害活性IC$_{50}$（μM）
(41)	0.27	(71)	0.22
(42)	0.44	(72)	0.20
(43)	0.52	(73)	0.43
(44)	0.95	(74)	0.42
(45)	0.62	(75)	0.17
(46)	0.81	(76)	0.14
(47)	2.00	(77)	0.19
(48)	1.50	(78)	0.14
(49)	0.85	(79)	0.11
(50)	0.22	(80)	0.33
(51)	0.32	(81)	0.58
(52)	0.90	(82)	1.21
(53)	1.30	(83)	0.51
(54)	1.30		
(55)	0.70		
(61)	0.41		
(62)	0.44		
(63)	0.99		
(64)	0.29		
(65)	1.20		
(66)	1.20		
(67)	0.61		
(68)	1.30		
(69)	0.47		
(70)	0.30		

【０１４７】（試験例２）血小板凝集抑制作用の測定
ウサギ多血小板血漿の調製及び血小板凝集の測定は、ＢｏｒｎとＣｒｏｓｓ（Ｊ．Ｐｈｙｓｔｏｌ．１６８，１７８～１９５（１９６３））の方法に従って行った。即ち、日本白色種ウサギ頸動脈より、無麻酔下、３．８％クエン酸ナトリウム溶液１容量に対し、９容量採血した。直ちに、２００×ｇ，２０℃，１５分間遠心分離し上清の多血小板血漿（以下、ＰＲＰと略す）を得た。ＰＲＰは、自動血球計数機（日本光電：ＭＥＫ－４１５０）で血小板数を測定し、１μｌあたり５５×１０^{4}個以上のものを使用した。

【０１４８】血小板凝集抑制作用は、ＰＲＰ２００μｌに対して被験薬溶液１０μｌを加え、３７℃で５分間加温後、２２μｇ／mlコラーゲンを１０μｌ添加して血小板の凝集反応をアグリコメーター（ＮＫＫ，ＰＡＴ－４Ａ）を用いて測定した。同時に、被験薬溶液の代わりに、被験薬溶解用溶媒のみを用いた時を最大凝集率１００％として被験薬群の抑制率を求めると共に５０％阻害に必要な量〔ＩＣ$_{50}$〕をプロビット法より算出した。

【０１４９】但し、被験薬は、ジメチルスルホオキシド及びポリオキシエチレン６０硬化ヒマシ油／エタノール溶液（１：１）に溶解し、生理食塩水で希釈して使用した。また、ジメチルスルホオキシド及びポリオキシエチレン６０硬化ヒマシ油は、それぞれ最終濃度が１％以下になる様に調製した。各実施例で製造した化合物を被験薬とし、測定結果を表２に示す。

【０１５０】
【表２】

化合物	血小板凝集抑制活性IC_{50}（μM）
(41)	56.0
(42)	94.0
(43)	52.0
(44)	60.0
(45)	56.0
(46)	83.0
(50)	25.0
(51)	88.0
(52)	61.0
(55)	44.0
(61)	9.40
(62)	21.0
(63)	23.0
(64)	28.0
(67)	18.0
(69)	13.0
(70)	9.60
(72)	54.0
(73)	9.20
(76)	11.0
(83)	28.0

【０１５１】（試験例３）カルパイン以外のプロテアーゼ阻害活性の測定

① 抗トリプシン活性の測定

抗トリプシン活性の測定は、Ａｏｙａｇｉ（Ｊ．Ａｎｔｉｂｉｏｔｉｃｓ，２２，５５８～５６８（１９６９）等の方法を一部改良して行った。

【０１５２】２％カゼイン溶液０．５ml，５０ｍＭ塩化カルシウム０．０５ml，被験薬溶液（１０％ジメチルスルホオキシド含有）０．０５ml，精製水０．１ml及び７０ｍＭホウ酸緩衝液（pH７．４）０．２５mlを含む混合液を３７℃で３分間加温した。その後０．１mg／mlトリプシン溶液を加えて反応を開始した。３７℃，３０分間反応した後、１．７Ｎ過塩素酸１mlを加えて反応を停止した。６０分間室温で放置した後、３，０００rpm，１０分間遠心分離した後上清の２８０ｎｍの吸光度（ａ）を測定した。同時に被験薬溶液の代わりに１０％ジメチルスルホオキシド溶液のみを用いた盲検の吸光度（ｂ）を測定した。トリプシン阻害率は次式〔（ｂ－ａ）／ｂ〕×１００により計算した。

【０１５３】実施例で製造した化合物（６１），（６３），（７６）及び（８３）を被験薬とした。

【０１５４】いずれの化合物も１０^{-4}Ｍの濃度で阻害活性を示さなかった。

【０１５５】② 抗α－キモトリプシン活性の測定

抗α－キモトリプシン活性の測定は、Ｅｒｌａｎｇｅｒ，Ｂ．Ｆ．（Ａｃｈ．Ｂｉｏｃｈｅｍ．Ｂｉｏｐｈｙｓ．１１５，２０６－２１０（１９６６）等の方法を一部改良して行った。即ち、１０ｍＭグルタリル－Ｌ－フェニルアラニン－ｐ－ニトロアニリド溶液（１０％ジメチルスルホオキシド－１０％ポリオキシエチレン６０硬化ヒマシ油含有）０．０５ml，５０ｍＭ塩化カルシウム溶液０．１ml，精製水０．２５ml，被験薬溶液（１０％ジメチルスルホオキシド－１０％ポリオキシエチレン６０硬化ヒマシ油含有）０．０５ml及び１００ｍＭトリス塩酸緩衝液（pH７．８）０．５mlを含む混合液を２５℃で３分間加温した。その後、２mg／mlα－キモトリプシン（タイプ－II）を加えて反応を開始し、直ちに２５℃での４０５nmの吸光度の増加を経時的に測定して１分間当りの吸光度の変化率（ａ）を求めた。同時に、被験薬溶液の代わりに１０％ジメチルスルホオキシド－１０％ポリオキシエチレン６０硬化ヒマシ油溶液のみを用いた盲検の１分間当りの吸光度の変化率（ｂ）を測定した。α－キモトリプシン阻害率は次式〔（ｂ－ａ）／ｂ〕×１００により計算し、５０％阻害に必要な量〔IC_{50}〕をプロビット法より算出した。比較として特開平１－１２１２５７号で製造された化合物ＳＵＡＭ－１４５４１

を用い測定を行った。結果を表３に示す。

【０１５６】

【表３】

被験薬	阻害活性：IC_{50}
化合物（6）	＞10^{-4}M
SUAM－14541	2．1×10^{-5}M

【０１５７】

【発明の効果】本発明の前記一般式（Ｉ）で表わされるアルデヒド誘導体は、選択的なカルパイン活性阻害作用及び血小板凝集抑制作用を示す。そのためカルパインの活性異常により引き起こされる虚血性疾患の治療に用いることが期待できる。

【手続補正書】

【提出日】平成５年２月１６日

【手続補正１】

【補正対象書類名】明細書

【補正対象項目名】０１５６

【補正方法】変更

【補正内容】

【０１５６】

【表３】

被験薬	阻害活性：IC_{50}
化合物（６１）	＞10^{-4}M
ＳＵＡＭ－１４５４１	２．1×10^{-5}M

フロントページの続き

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(54) **Aldehyde derivatives and their use as calpain inhibitors.**

(57) Aldehyde derivatives with a specific calpain inhibiting activity and a platelet-aggregation inhibiting effect with formula (I) or formula (II):

$$\text{Z-CONH-}\underset{}{\overset{\text{CHO}}{\overset{|}{\text{CH}}}}\text{-(CH}_2\text{)}_n\text{-R}^1 \qquad \text{(I)}$$

wherein R^1 represents an aromatic hydrocarbon group, a heterocyclic group, or a group of $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group; Z represents R^4-Y- or $R^6O-CH(R^5)-$ in which Y represents a 3- to 7-membered nitrogen-containing saturated heterocyclic group, or a single cyclic saturated hydrocarbon group, R^4 represents an alkyl group, an alkenyl group, an alkynyl group, an acyl group, a sulfonyl group, an alkoxycarbonyl group, a

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carbamoyl group, or a thiocarbamoyl group, R^5 represents hydrogen, an alkyl group, or an aromatic hydrocarbon group, and R^6 represents an acyl group, a carbamoyl group, a thiocarbamoyl group, or an alkyl group; and n is an integer of 1 to 5.

$$R^{10}\text{-}\underset{\displaystyle R^9}{\overset{|}{N}}\text{-}\underset{}{CH(R^8)}\text{-CONH-}CH(CHO)\text{-}(CH_2)_n\text{-}X\text{-}R^7 \qquad (II)$$

wherein R^7, R^8, R^9, and R^{10} are defined in the specification.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to aldehyde derivatives which serve as calpain inhibitors including a non-natural amino acid structure, and more particularly to aldehyde derivatives with a specific calpain inhibiting effect (i.e., inhibitory effect on the activity of calpain) and a platelet-aggregation inhibiting effect for increasing the curative effect of ischemic diseases.

Discussion of Background

Calpain is a proteolytic enzyme (cysteine protease) which can be activated by the calcium ion, and is widely present in the cells of vital tissues. Calpain is known to have physiological roles such as the histodialysis of tissues whose substrates are, for instance, myoprotein, zymoprotein, receptor protein and cytoskeleton protein, the activation of an inactivated enzyme precursor, and intracellular processing as described in Trends in Pharmacological Science Vol. 11, 139(1990).

It is reported that the abnormal acceleration of the enzyme activity of calpain in vivo may cause inveterate diseases such as ischemic diseases, inflammation, progressive muscular dystrophy, cataract, hypoimmunity, and essential hypertension.

It is considered that in ischemic diseases, calpain is sufficiently activated by the increase in the amount of the calcium ion in the cells during ischemia to cause cellular impairment and necrosis.

Conventional remedies for such ischemic diseases are calcium antagoists and β-blockers which have a vasodilation effect. However these remedies are not effective for curing and/or prophyaxis of the cellular impairment and necrosis in ischemic diseases.

Calpain inhibitors are therefore considered to be useful as remedies for such inveterate diseases. Conventionally known calpain inhibitors are compounds with a peptide structure, such as compounds with a dipeptide structure as disclosed in Japanese Laid-Open Patent Applications 1-121257, 2-268145, and Journal of Medicinal Chemistry 33, 11 (1990), compounds with a tripeptide structure as disclosed in Japanese Laid-Open Patent Applications 58-116616, 60-28990, and 61-103897, compounds with a tetrapeptide structure as disclosed in Japanese Laid-Open Patent Application 58-198453, and compounds with a pentapeptide structure as disclosed in Japanese Laid-Open Patent Application 61-10600.

However, the above-mentioned compounds which have capability of inhibiting the calpain activity do not have satisfactory effects in the treatment of the inveterate diseases. This is because each of the above compounds has a natural amino acid structure therein and can be cleaved by the proteolytic enzyme in vivo.

Furthermore, the following compounds are conventionally known as calpain inhibitors: epoxy succinic acid derivatives (J. Biochem., 87,339(1980)), piperazine derivatives (Japanese Laid-Open Patent Applications 57-169478, 58-126879, and 63-25575), aminoaldehyde derivatives (Japanese Laid-Open Patent Applications 61-103997, 1-12157, and 2-268145), and aminoaldehyde derivatives and amino ketone derivatives (Japanese Laid-Open Patent Application 2-256654). Of these compounds, the piperazine derivatives are reported to have a myocardium protecting effect. It is therefore considered that such piperazine derivatives may probably be used as remedies for ischemic diseases. However, those piperazine derivatives do not have a sufficient myocardium protection effect and a calpain inhibiting effect for use as remedies for ischemic diseases. The compounds other than the piperazine derivatives cannot be used satisfactorily as remedies for ischemic diseases although they have a calpain inhibiting effect.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide compounds which do not have a natural amino acid structure, but have a specific calpain inhibiting activity and a platelet-aggregation inhibiting effect for increasing the curative effect of ischemic diseases.

This object of the present invention can be achieved by aldehyde derivatives represented by the following formula (I):

$$\begin{array}{c} \text{CHO} \\ | \\ \text{Z-CONH-CH-(CH}_2\text{)}_n\text{-R}^1 \end{array} \qquad \text{(I)}$$

wherein R^1 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, or a group of $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group having 1 to 10 carbon atoms; Z represents R^4-Y- or $R^6O-CH(R^5)-$ in which Y represents a 3- to 7-membered nitrogen-containing saturated heterocyclic group, or a monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms, R^4 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an acyl group, a sulfonyl group, an alkoxycarbonyl group, a carbamoyl group, or a thiocarbamoyl group, R^5 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group, and R^6 represents an acyl group, a carbamoyl group, a thiocarbamoyl group, or an alkyl group having 1 to 10 carbon atoms; and n is an integer of 1 to 5.

The above object of the present invention can also be achieved by aldehyde derivatives represented by the following formula (II):

$$\begin{array}{c} \text{R}^9\ \text{R}^8 \qquad\qquad \text{CHO} \\ |\quad\ | \qquad\qquad\quad | \\ \text{R}^{10}\text{-N-CH-CONH-CH-(CH}_2\text{)}_n\text{-X-R}^7 \end{array}$$

wherein R^7 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms with a substituent, or a cyclic alkyl group having 3 to 6 carbon atoms; R^8 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group; R^9 represents hydrogen, or an alkyl group having 1 to 10 carbon atoms; R^{10} represents an alkoxycarbonyl group, an acyl group, a carbamoyl group, or a sulfonyl group; X represents oxygen, or a group represented by $-S(O)_m-$ in which m is 0, 1 or 2; and n is an integer of 1 to 5.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the aldehyde derivatives of the present invention having the previously mentioned formula (I), R^1 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, or a group represented by $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group having 1 to 10 carbon atoms.

Examples of the aromatic hydrocarbon group represented by R^1 are phenyl group, naphthyl group and anthranyl group.

Examples of the heterocyclic group represented by R^1 are furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

The alkyl group represented by R^1 may be a substituted or unsubstituted straight-chain, branched or cyclic alkyl group having 1 to 10 carbon atoms. Specific examples of the alkyl group represented by R^1 are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group. Examples of the substituent of the substituted alkyl group include the previously mentioned aromatic hydrocarbon group and heterocyclic group.

The alkenyl group represented by R^1 may be a substituted or unsubstituted straight-chain, branched or cyclic alkenyl group having 2 to 10 carbon atoms. Specific examples of the alkenyl group represented by R^1 are ethenyl or vinyl group, 1-propenyl group, 2-propenyl group, iso-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-2-propenyl group, 1-pentenyl group, 1-hexenyl group, 1-heptenyl group, 1-cyclohexenyl group and 2-cylcohexenyl group. Examples of the substituent of the substituted alkenyl group are the previously mentioned aromatic hydrocarbon group and heterocyclic group.

Moreover, the aromatic hydrocarbon group and the heterocyclic group represented by R^1 in the

previously mentioned formula (I), and the aromatic hydrocarbon group and the heterocyclic group which are the substituents of the alkyl group or the alkenyl group represented by R^1 may have a substituent. Specific examples of the substituent are an alkyl group having 1 to 10 carbon atoms such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, and heptyl group; an alkoxyl group having 1 to 10 carbon atoms such as methoxy group, ethoxy group, propoxy group, butoxy group, and benzyloxy group; a halogen atom such as fluorine, chlorine, bromine and iodine; an amino group such as amino group, dimethylamino group, and diethylamino group; hydroxyl group; and a nitro group.

R^1 in formula (I) may also be a group represented by $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group having 1 to 10 carbon atoms. Examples of the aromatic hydrocarbon group, the heterocyclic group and the alkyl group represented by R^3 are respectively the same as those represented by R^1 in formula (I). The alkyl group represented by R^3 may have as a substituent the same aromatic hydrocarbon group or heterocyclic group represented by R^1.

Z in formula (I) represents R^4-Y- in which Y represents a 3 to 7-membered nitrogen-containing saturated heterocyclic group, or a monocyclic saturated hydrocarbon having 3 to 7 carbon atoms, and R^4 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, which may be a straight-chain alkynyl group or a branched alkynyl group, an acyl group, a sulfonyl group, an alkoxycarbonyl group, a carbamoyl group, or a thiocarbamoyl group.

Examples of the 3- to 7-membered nitrogen-containing saturated heterocyclic ring represented by Y are aziridine, azetidine, pyrrolidine, piperidine, and perhydroazepine.

Examples of the 3- to 7-membered nitrogen-containing saturated heterocyclic group represented by Y are azetidine-1,2-diyl group, pyrrolidine-1,2-diyl group, pyrrolidine-1,3-diyl group, piperidine-1,2-diyl group, piperidine-1,3-diyl group, piperidine-1,4-diyl group, perhydroazepine-1,2-diyl group, perhydroazepine-1,3-diyl group, and perhydroazepine-1,4-diyl group.

Examples of the monocyclic saturated hydrocarbon having 3 to 7 carbon atoms represented by Y are cyclopropane, cyclobutane, cyclopentane, and cycloheptane.

Examples of the corresponding monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms are

1,2-cyclobutylene group, 1,3-cyclobutylene group,
1,2-cyclopentylene group, 1,3-cyclopentylene group,
1,2-cyclohexylene group, 1,3-cyclohexylene group,
1,4-cyclohexylene group, 1,2-cycloheptylene group,
1,3-cycloheptylene group, and 1,4-cycloheptylene group.

The alkyl group represented by R^4 is a straight-chain, branched, or cyclic alkyl group having 1 to 10 carbon atoms, which may be the same represented by R^1. More specifically, examples of the alkyl group represented by R^4 are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyly group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

The alkyl group represented by R^4 may have a substituent such as an aromatic hydrocarbon group or a heterocyclic group, which may be the same substituent as for the alkyl group represented by R^1.

The aromatic hydrocarbon group or the heterocyclic group which is the substituent for the above alkyl group may further have a substituent. Specific examples of the substituent are an alkyl group having 1 to 10 carbon atoms such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, and heptyl group; an alkoxyl group having 1 to 10 carbon atoms such as methoxy group, ethoxy group, propoxy group, butoxy group, and benzyloxy group; a halogen atom such as fluorine, chlorine, bromine and iodine; an amino group such as amino group, dimethylamino group, and diethylamino group; a hydroxyl group; and a nitro group.

The alkenyl group represented by R^4 is a straight-chain, branched or cyclic alkenyl group having 2 to 10 carbon atoms, which may have a substituent and is the same alkenyl group as represented by R^1. More specifically, examples of the alkenyl group represented by R^4 are vinyl group, 1-propenyl group, 2-propenyl group, iso-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-2-propenyl group, 1-pentenyl group, 1-hexenyl group, 1-heptenyl group, 1-cyclohexenyl group and 2-cyclohexenyl group. Examples of the substituent of the alkenyl group represented by R^4 are the same aromatic hydrocarbon group or heterocyclic group as represented by R^1. The aromatic hydrocarbon group or the heterocyclic group may further have any of the same substituents as in the alkyl group represented by R^4.

Examples of the alkynyl group having 2 to 10 carbon atoms represented by R^4 are 2-propynyl group, 1-

propynyl group, 1-butynyl group, 2-butynyl group, 1-pentynyl group, 1-hexynyl group, 1-heptynyl group, 1-optynyl group, 1-nonyl group, 1-denyl group and 1-methyl-2-propynyl group.

Examples of the acyl group represented by R^4 are acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cyclohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluoyl group, 1-(benzyloxycarbonyl)piperidine-4-carbonyl group, cinnamoyl group, phenylacetyl group, 2-thienylcarbonyl group, trimethyl acetyl group, cyclopentane carbonyl group, 2,6-dichlorobenzoyl group, 3,4-dichlorobenzoyl group, 4-phenylbenzoyl group, 2-chlorocinnamoyl group, 3-chlorocinnamoyl group, 4-chlorocinnamoyl group, 2-nitrocinnamoyl group, indolyl-2-carbonyl group, indolyl-3-carbonyl group, quinolyl-2-carbonyl group, quinolyl-3-carbonyl group, isoquinolyl-3-carbonyl group, diphenyl acetyl group, fluorenyl-9-carbonyl group, 3-phenylpropionyl group, 4-phenyl-butyryl group, 3-(3-pyridyl)acryloyl group, 3-(3-thienyl)acryloyl group, 3-phenyl-2-methylacryloyl group, 3-(2-naphthyl)acryloyl group; (2S)-3-phenyl-2-(benzyloxycarbonylamino)propionyl group, and (2R)-3-phenyl-2-(benzyloxycarbonylamino)propionyl group.

The sulfonyl group represented by R^4 may have a substituent such as an alkyl group or an aromatic hydrocarbon group. Specific examples of the sulfonyl group represented by R^4 are methane sulfonyl group, ethane sulfonyl group, propane sulfonyl group, butane sulfonyl group, pentane sulfonyl group, hexane sulfonyl group, trifluoromethane sulfonyl group, benzene sulfonyl group, naphthalene sulfonyl group, 4-methyl benzene sulfonyl group, iso-quinoline-5-sulfonyl group, and quinoline-8-sulfonyl group.

The alkoxycarbonyl group represented by R^4 is a substituted or unsubstituted, saturated or unsaturated alkoxycarbonyl group. Specific examples of the alkoxycarbonyl group represented by R^4 are methoxy carbonyl group, ethoxy carbonyl group, propoxy carbonyl group, butoxy carbonyl group, pentyloxy carbonyl group, hexyloxy carbonyl group, heptyloxy carbonyl group, octyloxy carbonyl group, nonyloxy carbonyl group, decyloxy carbonyl group, iso-propoxy carbonyl group, iso-butoxy carbonyl group, s-butoxy carbonyl group, t-butoxy carbonyl group, iso-pentyloxy carbonyl group, neopentyloxy carbonyl group, t-pentyloxy carbonyl group, iso-hexyloxy carbonyl group, cinnamyloxy carbonyl group, and benzyloxy carbonyl group.

The carbamoyl group represented by R^4 may have a substituent, such as the so far mentioned substituted or unsubstituted alkyl group or substituted or unsubstituted aromatic hydrocarbon group. Examples of the carbamoyl group represented by R^4 are N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)carbamoyl group, N-(3-chlorophenyl)carbamoyl, N-(4-chlorophenyl)carbamoyl, N-(1-naphthyl)carbamoyl group, and N-benzylcarbamoyl group.

The thiocarbamoyl group represented by R^4 may have a substituent. Examples of the substituent are a substituted or unsubstituted alkyl group and a substituted or unsubstituted aromatic hydrocarbon group. Examples of the thiocarbamoyl group represented by R^4 are N-methylthiocarbamoyl group, N-ethylthiocarbamoyl group, N-phenylthiocarbamoyl group, N-(2-chlorophenyl)thiocarbamoyl group, N-(1-naphthyl)-thiocarbamoyl group, N-(1-naphthyl)thiocarbamoyl group, and N-benzylthiocarbamoyl group.

Z also represents $R^6O\text{-}CH(R^5)\text{-}$ in which R^5 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group, and R^6 represents an acyl group, a carbamoyl group, a thiocarbamoyl group, or an alkyl group having 1 to 10 carbon atoms.

The alkyl group represented by R^5 may be a straight-chain, branched or cyclic alkyl group having 1 to 10 carbon atoms. Specific examples of the alkyl group are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

Examples of the aromatic hydrocarbon group represented by R^5 are phenyl group, naphthyl group and anthranyl group, which are the same as those represented by R^1 in formula (I).

The alkyl group represented by R^5 may have a substituent. Examples of the substituent are the aromatic-hydrocarbon group and heterocyclic group represented by R^1 in formula (I).

Examples of the acyl group represented by R^6 are acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cylcohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluoyl group, and 1-(benzyloxycarbonyl)piperidine-4-carbonyl group.

The carbamoyl group represented by R^6 may have a substituent. Examples of the carbamoyl group are N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)-carbamoyl group, N-(1-naphthyl)carbamoyl group and N-benzylcarbamoyl group.

The thiocarbamoyl group represented by R^6 may have a substituent. Examples of the thiocarbamoyl group are N-methylthiocarbamoyl group, N-ethylthiocarbamoyl group, N-phenylthiocarbamoyl group, N-(2-chlorophenyl)thiocarbamoyl group, N-(2-naphthyl)thiocarbamoyl group and N-benzylthiocarbamoyl group.

The alkyl group represented by R^6 is the same as the alkyl group represented by R^5 and may have a substituent. Specifically, examples of the alkyl group represented by R^6 are methyl group, ethyl group,

propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group. Examples of the substituent of the alkyl group are the aromatic hydrocarbon group and heterocyclic group represented by R^1 in formula (I).

The object of the present invention can also be achieved by aldehyde derivatives represented by the following formula (II):

$$R^{10}-\overset{R^9}{\overset{|}{N}}-\overset{R^8}{\overset{|}{C}}H-CONH-\overset{CHO}{\overset{|}{C}}H-(CH_2)_n-X-R^7 \qquad (II)$$

wherein R^7 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms, which has a substituent such as an aromatic hydrocarbon group, and a heterocyclic group, or a cyclic alkyl group having 3 to 6 carbon atoms; R^8 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group; R^9 represents hydrogen, or an alkyl group having 1 to 10 carbon atoms; R^{10} represents an alkoxycarbonyl group, an acyl group, a carbamoyl group, or a sulfonyl group; X represents oxygen, or a group represented by $-S(O)_m-$ in which m is 0, 1 or 2; and n is an integer of 1 to 5.

Examples of the aromatic hydrocarbon group represented by R^7 are phenyl group, naphthyl group and anthranyl group.

Examples of the heterocyclic group represented by R^7 are furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

The substituted alkyl group represented by R^7 is a substituted straight-chain or branched alkyl group having 1 to 10 carbon atoms. Specific examples of the alkyl group represented by R^7 are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, and iso-hexyl group.

Examples of the cyclic alkyl group having 3 to 6 carbon atoms represented by R^7 are cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

Moreover, the aromatic hydrocarbon group and the heterocyclic group represented by R in formula (II), and the aromatic hydrocarbon group and the heterocyclic group which are the substituents of the alkyl group represented by R^7 may have a substituent. Specific examples of the substituent are an alkyl group having 1 to 10 carbon atoms such as methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, and iso-hexyl group; an alkoxyl group having 1 to 10 carbon atoms such as methoxy group, ethoxy group, propoxy group, butoxy group, pentyloxy group, hexyloxy group, butyloxy group, octyloxy group, nonyloxy group, decyloxy group, iso-propoxy group, iso-butoxy group, s-butoxy group, t-butoxy group, iso-pentyloxy group, neopentyloxy group, t-pentyloxy group and iso-hexyloxy group, and benzyloxy group; a halogen atom such as fluorine, chlorine, bromine and iodine; an amino group such as amino group, dimethylamino group, and diethylamino group; hydroxyl group; and a nitro group.

R^8 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group.

The alkyl group represented by R^8 may be a straight-chain or branched alkyl group having 1 to 10 carbon atoms. Specific examples of the alkyl group are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, and iso-hexyl group. The alkyl group represented by R^8 may have a substituent such as the aromatic hydrocarbon group and heterocyclic group represented by R^7.

Examples of the aromatic hydrocarbon group represented by R^8 are the same as those represented by R^7 in formula (II). Specifically, examples of the aromatic hydrocarbon group represented by R^8 are phenyl group, naphthyl group and anthranyl group.

R^9 represents hydrogen or an alkyl group having 1 to 10 carbon atoms. The alkyl group represented by R^9 may be the same as represented by R^8. More specifically, the alkyl group represented by R^9 may be a straight-chain or branched alkyl group having 1 to 10 carbon atoms. Specific examples of the alkyl group

are methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, iso-butyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, and iso-hexyl group. The alkyl group represented by R^9 may have a substituent such as the aromatic hydrocarbon group and heterocyclic group represented by R^7.

As mentioned above, R^{10} represents an alkoxy carbonyl group, an acyl group, a carbamoyl group or a sulfonyl group.

Specific examples of the alkoxy carbonyl group represented by R^{10} are methoxy carbonyl group, ethoxy carbonyl group, propoxy carbonyl group, butoxy carbonyl group, pentyloxy carbonyl group, hexyloxy carbonyl group, heptyloxy carbonyl group, octyloxy carbonyl group, nonyloxy carbonyl group, decyloxy carbonyl group, iso-propoxy carbonyl group, iso-butoxy carbonyl group, s-butoxy carbonyl group, t-butoxy carbonyl group, iso-pentyloxy carbonyl group, neopentyloxy carbonyl group, t-pentyloxy carbonyl group, iso-hexyloxy carbonyl group, cinnamyloxy carbonyl group, and benzyloxy carbonyl group.

Examples of the acyl group represented by R^{10} are acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cyclohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluoyl group, and 1-(benzyloxycarbonyl)piperidine-4-carbonyl group.

The carbamoyl group represented by R^{10} may have a substituent. Examples of the carbamoyl group are N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)-carbamoyl group, N-(1-naphthyl)carbamoyl group and N-benzylcarbamoyl group.

Examples of the sulfonyl group represented by R^{10} are methane sulfonyl group, ethane sulfonyl group, propane sulfonyl group, butane sulfonyl group, pentane sulfonyl group, hexane sulfonyl group, trifluoromethane sulfonyl group, benznenesulfonyl group, 4-methylbenzene sulfonyl group, isoquinoline-5-sulfonyl group, and quinoline-8-sulfonyl group.

Aldehyde derivatives (I) of the present invention, which are represented by the previously mentioned formula (I) in which Z is R^4-Y-, more specifically represented by the following formula (IA), can be prepared in accordance with the following reaction scheme:

$$R^4\text{-Y-CONH-}\underset{}{\overset{\displaystyle \text{CHO}\atop |}{\text{CH}}}\text{-(CH}_2)_n\text{-}R^1 \qquad \text{(IA)}$$

wherein R^1 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, or a group of -X-R^3 in which X represents O, -S(O)$_m$- (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group having 1 to 10 carbon atoms; R^4 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an acyl group, a sulfonyl group, an alkoxycarbonyl group, a carbamoyl group, or a thiocarbamoyl group; and n is an integer of 1 to 5.

$$\underset{\text{(IA-1)}}{R^4\text{-Y-COOH}} \quad + \quad \underset{\text{(IA-2)}}{H_2N\text{-}\overset{\displaystyle CH_2OH}{\overset{|}{C}H}\text{-}(CH_2)_n\text{-}R^1} \xrightarrow{}$$

(Step I-1)

$$\underset{\text{(IA-3)}}{R^4\text{-Y-CONH-}\overset{\displaystyle CH_2OH}{\overset{|}{C}H}\text{-}(CH_2)_n\text{-}R^1} \text{ (IA-3)} \xrightarrow[\text{(Step I-1)}]{\text{Oxidation}}$$

$$\underset{\text{(IA)}}{R^4\text{-Y-CONH-}\overset{\displaystyle CHO}{\overset{|}{C}H}\text{-}(CH_2)_n\text{-}R^1}$$

wherein R^1, R^4, Y, and n are respectively the same as in formula (I).

[Step I-1]

In this step, a carboxylic acid derivative of formula (IA-1) is allowed to react with an amine derivative of formula (IA-2), so that an alcohol derivative of formula (IA-3) is produced.

Specific examples of the carboxylic acid derivative of formula (IA-1) are as follows:
1-benzyl-piperidine-4-carboxylic acid,
1-(2-naphthylmethyl)piperidine-4-carboxylic acid,
1-(3,4-dichlorobenzyl)piperidine-4-carboxylic acid,
1-cinnamylpiperidine-4-carboxylic acid,
1-benzoylpiperidine-4-carboxylic acid,
1-phenylacetylpiperidine-4-carboxylic acid,
1-(3-phenylpropionyl)piperidine-3-carboxylic acid,
1-(3-phenylpropionyl)piperidine-4-carboxylic acid,
1-(4-phenylbutyryl)piperidine-4-carboxylic acid,
1-cinnamoylpyrrolidine-2-carboxylic acid,
1-cinnamoylpyrrolidine-3-carboxylic acid,
1-cinnamoylpyrrolidine-4-carboxylic acid,
1-(1-naphthoyl)piperidine-3-carboxylic acid,
1-(2-naphthoyl)piperidine-3-carboxylic acid,
1-(1-naphthoyl)piperidine-4-carboxylic acid,
1-(2-naphthoyl)piperidine-4-carboxylic acid,
1-(2-naphthoyl)pyrrolidine-2-carboxylic acid,
1-(2-naphthoyl)azetidine-2-carboxylic acid,
1-(2-naphthoyl)perhydroazepine-3-carboxylic acid,
1-(2-naphthoyl)perhydroazepine-4-carboxylic acid,
1-(2-thienylcarbonyl)piperidine-4-carboxylic acid,
1-(3-pyridylcarbonyl)piperidine-3-carboxylic acid,
1-acetylpiperidine-4-carboxylic acid,
1-trimethylacetylpiperidine-4-carboxylic acid,
1-diphenylacetylpiperidine-4-carboxylic acid,
1-(9-fluorenylcarbonyl)piperidine-4-carboxylic acid,
1-(2,6-dichlorobenzoyl)piperidine-4-carboxylic acid,

1-(3,4-dichlorobenzoyl)piperidine-3-carboxylic acid,
1-(3,4-dichlorobenzoyl)piperidine-4-carboxylic acid,
1-(2-chlorocinnamoyl)piperidine-2-carboxylic acid,
1-(2-chlorocinnamoyl)piperidine-3-carboxylic acid,
1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid,
1-(2-chlorocinnamoyl)pyrrolidine-3-carboxylic acid,
1-(3-chlorocinnamoyl)piperidine-4-carboxylic acid,
1-(4-chlorocinnamoyl)piperidine-3-carboxylic acid,
1-(4-chlorocinnamoyl)piperidine-4-carboxylic acid,
1-(2-chlorocinnamoyl)perhydroazepine-3-carboxylic acid,
1-(2-chlorocinnamoyl)perhydroazepine-4-carboxylic acid,
1-(cyclopentylcarbonyl)azetidine-3-carboxylic acid,
1-(cyclopentylcarbonyl)piperidine-4-carboxylic acid,
1-(cyclohexylcarbonyl)piperidine-4-carboxylic acid,
1-(methylsulfonyl)azetidine-3-carboxylic acid,
1-(ethylsulfonyl)pyrrolidine-2-carboxylic acid,
1-(trifluoromethylsulfonyl)piperidine-4-carboxylic acid,
1-(4-methylphenylsulfonyl)piperidine-3-carboxylic acid,
1-(4-methylphenylsulfonyl)piperidine-4-carboxylic acid,
1-(1-naphthylsulfonyl)pyrrolidine-3-carboxylic acid,
1-(2-naphthylsulfonyl)pyrrolidine-3-carboxylic acid,
1-(2-naphthylsulfonyl)piperidine-3-carboxylic acid,
1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid,
1-(2-naphthylsulfonyl)perhydroazepine-3-carboxylic acid,
1-(2-naphthylsulfonyl)perhydroazepine-4-carboxylic acid,
1-benzyloxycarbonylazetidine-2-carboxylic acid,
1-benzyloxycarbonylpyrrolidine-2-carboxylic acid,
1-benzyloxycarbonylpiperidine-2-carboxylic acid,
1-benzyloxycarbonylpiperidine-3-carboxylic acid,
1-benzyloxycarbonylpiperidine-4-carboxylic acid,
1-ethoxycarbonylpiperidine-4-carboxylic acid,
1-(t-butoxycarbonyl)piperidine-3-carboxylic acid,
1-cinnamyloxycarbonylpiperidine-3-carboxylic acid,
1-cinnamyloxycarbonylpiperidine-4-carboxylic acid,
1-cinnamyloxycarbonylpyrrolidine-3-carboxylic acid,
1-(N-benzylcarbamoyl)piperidine-3-carboxylic acid,
1-(N-benzylcarbamoyl)piperidine-4-carboxylic acid,
1-(N-phenylcarbamoyl)pyrrolidine-3-carboxylic acid,
1-(N-phenylcarbamoyl)piperidine-2-carboxylic acid,
1-(N-phenylcarbamoyl)piperidine-3-carboxylic acid,
1-(N-phenylcarbamoyl)piperidine-4-carboxylic acid,
1-[N-(2-chlorophenyl)carbamoyl]piperidine-4-carboxylic acid,
1-[N-(3-chlorophenyl)carbamoyl]piperidine-4-carboxylic acid,
1-[N-(4-chlorophenyl)carbamoyl]piperidine-4-carboxylic acid,
1-[N-(2-naphthyl)carbamoyl]piperidine-3-carboxylic acid,
1-[N-(2-naphthyl)carbamoyl]piperidine-4-carboxylic acid,
1-[N-(2-naphthyl)carbamoyl]perhydroazepine-3-carboxylic acid,
1-[N-(2-naphthyl)carbamoyl]perhydroazepine-4-carboxylic acid,
1-(N-phenylthiocarbamoyl)piperidine-3-carboxylic acid,
1-(N-phenylthiocarbamoyl)piperidine-4-carboxylic acid,
1-[N-(2-naphthyl)thiocarbamoyl]piperidine-3-carboxylic acid, and
1-[N-(2-naphthyl)thiocarbamoyl]piperidine-4-carboxylic acid.

The amine derivatives of formula (IA-2) are commercially available. However, they can be easily produced from the corresponding amino acids.

Specific examples of the amine derivative of formula (IA-2) are as follows:
(2S)-2-aminobutanol,
(2S)-2-amino-3-methylbutanol,
(2S)-2-aminopentanol,

(2S)-2-amino-4-methylpentanol,
(2S)-2-aminohexanol,
(2S)-2-aminoheptanol,
(2S)-2-amino-3-phenylpropanol,
(2S)-2-amino-4-phenylbutanol,
(2S)-2-amino-5-phenylpentanol,
(2S)-2-amino-6-phenylhexanol,
(2S)-2-amino-7-phenylheptanol,
(2S)-2-amino-3-(2-fluorophenyl)propanol,
(2S)-2-amino-3-(4-hydroxyphenyl)propanol,
(2S)-2-amino-3-(4-benzyloxyphenyl)propanol,
(2S)-2-amino-3-(3-indolyl)propanol,
(2R)-2-amino-3-benzyloxypropanol,
(2R)-2-amino-3-benzylthiopropanol,
(2R)-2-amino-3-(2-fluorobenzylthio)propanol,
(2R)-2-amino-3-(4-chlorobenzylthio)propanol,
(2R)-2-amino-3-methylthiopropanol,
(2R)-2-amino-3-ethylthiopropanol,
(2S)-2-amino-4-phenyloxybutanol,
(2S)-2-amino-4-(3-chlorophenyloxy)butanol,
(2S)-2-amino-4-(4-chlorophenyloxy)butanol,
(2S)-2-amino-4-benzyloxybutanol,
(2S)-2-amino-4-ethoxybutanol,
(2S)-2-amino-4-methylthiobutanol,
(2S)-2-amino-4-phenylthiobutanol,
(2S)-2-amino-4-(4-chlorophenylthio)butanol,
(2S)-2-amino-4-benzylthiobutanol,
(2S)-2-amino-4-(2-chlorobenzylthio)butanol,
(2S)-2-amino-4-(4-chlorobenzylthio)butanol,
(2S)-2-amino-4-(2-fluorobenzylthio)butanol,
(2S)-2-amino-4-(1-thienylmethylthio)butanol,
(2S)-2-amino-4-(2-thienylmethylthio)butanol,
(2S)-2-amino-5-phenyloxypentanol,
(2S)-2-amino-5-(4-chlorophenyloxy)pentanol,
(2S)-2-amino-5-benzyloxypentanol,
(2S)-2-amino-5-ethoxypentanol,
(2S)-2-amino-5-methylthiopentanol,
(2S)-2-amino-5-phenylthiopentanol,
(2S)-2-amino-5-(4-chlorophenylthio)pentanol,
(2S)-2-amino-5-benzylthiopentanol,
(2S)-2-amino-5-(2-chlorobenzylthio)pentanol,
(2S)-2-amino-5-(4-chlorobenzylthio)pentanol,
(2S)-2-amino-5-(2-fluorobenzylthio)pentanol,
(2S)-2-amino-5-(1-thienylmethylthio)pentanol,
(2S)-2-amino-5-(2-thienylmethylthio)pentanol,
(2S)-2-amino-5-phenyl-4-pentene-1-ol,
(2S)-2-amino-5-(2-chlorophenyl)-4-pentane-1-ol,
(2S)-2-amino-4-phenyl-3-butene-1-ol, and
(2S)-2-amino-6-phenyl-5-hexene-1-ol.

The ester derivative with the following formula (IA-2a) can be used as the material in Step I-1 instead of the amino derivative of formula (IA-2):

$H_2N\text{-}CH(COOR)\text{-}(CH_2)_n\text{-}R^1$ (IA-2a)

In the case where the ester derivative of formula (IA-2a) is used in Step I-1, the product obtained contains an ester group therein. Therefore, it is necessary to reduce the ester group in order to convert the ester derivative of formula (IA-2a) into the alcohol derivative of formula (IA-3).

It is preferable that the reaction in Step I-1 be carried out in the presence of a condensation agent. As

the condensation agent, for instance, carbodiimide reagents such as dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC•HCl) can be employed. It is also preferable that the above-mentioned condensation agent be used in an amount of 1 to 3 equivalents, more preferably in an amount of 1.5 to 2 equivalents, with respect to the carboxylic acid derivative of formula (IA-1) or the amine derivative of formula (IA-2), in order to carry out the reaction efficiently.

Furthermore, it is preferable that the above reaction in Step A-1 be carried out in an inert solvent. Examples of the inert solvent are halogenated hydrocarbons such as dichloromethane, chloroform, and dichloroethane; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), and dioxane; amides such as dimethylformamide; dimethyl sulfoxide (DMSO); and acetonitrile. These inert solvents can be used alone or in combination.

The reaction proceeds in the temperature range of -50°C to the reflux temperature under atmospheric pressure. However, it is preferable that the reaction temperature be set in the range of -30°C to 30°C in order to carry out the reaction efficiently.

The carboxyl group in the carboxylic acid derivative of formula (IA-1) can be converted to, for example, an active ester group, a carboxylic acid halide group, or an acid anhydride group for use in the above reaction in Step I-1.

[Step I-2]

In this step, the alcohol derivative of formula (IA-3) obtained in the reaction of Step I-1 is oxidized, so that an aldehyde derivative of formula (IA) is produced.

When R^4 in the formula (IA-3) is an alkoxycarbonyl group or a substituted carbamoyl group, the alcohol derivative of formula (IA-3) can be produced by the reaction in Step A-1, as mentioned previously. However, it is also possible to produce the alcohol derivative of formula (IA-3) by allowing a compound having formula (IA-1b) to react with the amine derivative of formula (IA-2), and allowing the resultant compound to react with a corresponding alcohol or amine having the desired group:

HOOC-Y-COOH (IA-1b)

wherein Y is the same as in formula (I).

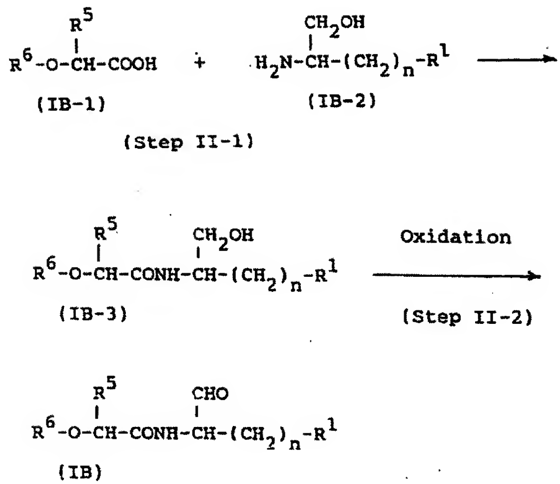
An active dimethyl sulfoxide (DMSO) oxidization method is employed for the oxidization in Step I-2. DMSO is an oxidizing agent and can be used in combination with an activating agent such as dicyclohexylcarbodiimide, phosphorus pentoxide, pyridine•sulfur trioxide complex, oxalyl chloride, acetic anhydride, and trifluoroacetic anhydride. It is preferable that the oxidization agent be employed in an amount of 1 to 4 equivalents to the alcohol derivative of formula (IA-3).

It is preferable that the above reaction in Step B-1 be carried out in a solvent. As the solvent, halogenated hydrocarbons such as dichloromethane, dichloroethane, and chloroform can be employed. Alternatively, DMSO employed as the oxidization agent can be used as the solvent for this reaction by using the same in an excessive amount. The above reaction in Step B-1 can be carried out at -20°C to 30°C.

Aldehyde derivatives (II) of the present invention, which are represented by the previously mentioned formula (I) in which Z is $R^6O\text{-}CH(R^5)$, more specifically represented by the following formula (IB), can be prepared in accordance with the following reaction scheme:

$$R^6O\text{-}CH(R^5)\text{-}CONH\text{-}\underset{}{\overset{\displaystyle CHO}{\overset{|}{CH}}}\text{-}(CH_2)_n\text{-}R^1 \qquad (IB)$$

wherein R^1 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, or a group of $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group, a heterocyclic group, or an alkyl group having 1 to 10 carbon atoms; R^5 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group, and R^6 represents an acyl group, a carbamoyl group, a thiocarbamoyl group, or an alkyl group having 1 to 10 carbon atoms; and n is an integer of 1 to 5.

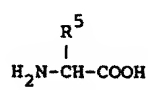


wherein R^5, R^6, and n are respectively the same as in formula (I).

[Step II-1]

In this step, a carboxylic acid derivative of formula (IB-1) is allowed to react with an amine derivative of formula (IB-2), which is the same as the amine derivative of formula (IA-2) employed in the preparation of aldehyde derivatives (I), whereby an alcohol derivative of formula (IB-3) is produced.

The carboxylic acid derivative of formula (IB-1) can be easily synthesized from the following amino compound:



Specific examples of the carboxylic acid derivative of formula (IB-1) are as follows:
(2S)-2-(3-phenylpropyloxy)-4-methylpentanoic acid,
(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid,
(2S)-2-(N-phenylthiocarbamoyloxy)-4-methylpentanoic acid,
(2S)-2-[N-(2-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-[N-(2-naphthyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-(N-t-butylcarbamoyloxy)-4-methylpentanoic acid,
(2S)-2-(N-benzylcarbamoyloxy)-4-methylpentanoic acid,
(2S)-2-[(3-phenylpropyl)carbonyloxy]-4-methylpentanoic acid,
(2S)-2-[N-(3,4-dichlorophenyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-[N-(3-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-[N-(4-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid,
(2S)-2-(N-n-propylcarbamoyloxy)-4-methylpentanoic acid,
(2S)-2-(4-phenylbutyloxy)-3-methylbutanoic acid,

(2S)-2-(N-phenylcarbamoyloxy)-3-methyl-butanoic acid,
(2S)-2-[N-(1-naphthyl)carbamoyloxy]-3-methylbutanoic acid,
(2S)-2-[N-(2-naphthyl)carbamoyloxy]-3-methylbutanoic acid,
(2S)-2-[N-(1-naphthyl)carbamoyloxy]-3-phenylpropanoic acid,
(2S)-2-[N-(2-naphthyl)carbamoyloxy]-3-phenylpropanoic acid,
(2S,3S)-2-(N-phenylcarbamoyloxy)-3-methylpentanoic acid,
(2S,3R)-2-(N-phenylcarbamoyloxy)-3-methylpentanoic acid,
(2S,3S)-2-[N-(1-naphthyl)carbamoyloxy)-3-methylpentanoic acid, and
(2S,3R)-2-[N-(1-naphthyl)carbamoyloxy]-3-methylpentanoic acid.

The amine derivatives of formula (IB-2) are commercially available. However, they can be easily produced from the corresponding amino acids.

It is preferable that the reaction in Step II-1 be carried out in the presence of a condensation agent. As the condensation agent, for instance, carbodiimide reagents such as dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC•HCl) can be employed. It is also preferable that the above-mentioned condensation agent be used in an amount of 1 to 3 equivalents, more preferably in an amount of 1.5 to 2 equivalents, with respect to the carboxylic acid derivative of formula (IB-1) or the amine derivative of formula (IB-2). In order to carry out the reaction efficiently.

Furthermore, it is preferable that the above reaction in Step II-1 be carried out in an inert solvent. Examples of the inert solvent are halogenated hydrocarbons such as dichloromethane, chloroform, and dichloroethane; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), and dioxane; amides such as dimethylformamide; dimethyl sulfoxide (DMSO); and acetonitrile. These inert solvents can be used alone or in combination.

The reaction proceeds in the temperature range of -50°C to the reflux temperature under atmospheric pressure. However, it is preferable that the reaction temperature be set in the range of -30°C to 30°C in order to carry out the reaction efficiently.

The carboxyl group in the carboxylic acid derivative of formula (IB-1) can be converted to, for example, an active ester group, a carboxylic acid halide group, or an acid anhydride group for use in the above reaction in Step II-1.

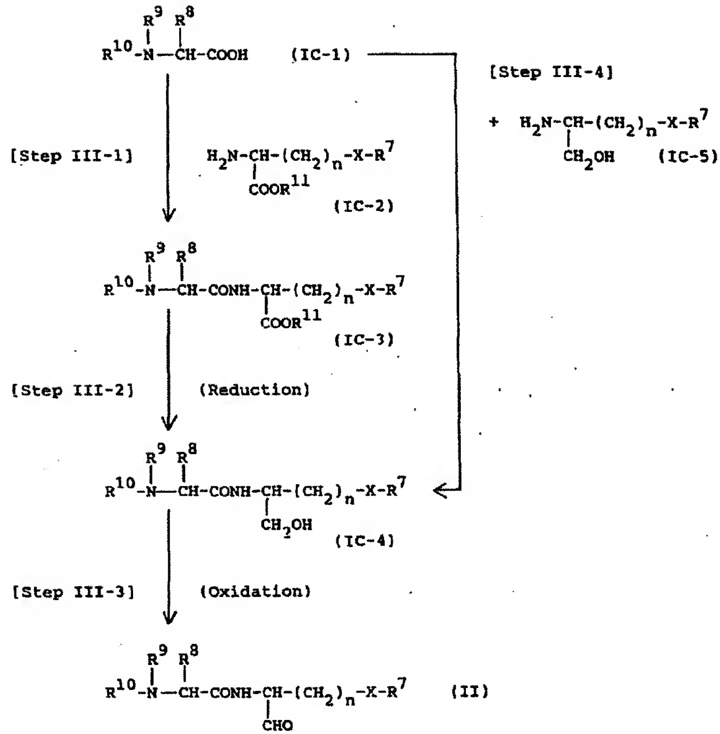
[Step II-2]

In this step, the alcohol derivative of formula (IB-3) obtained in the reaction of Step II-1 is oxidized, so that an aldehyde derivative of formula (IB) is produced.

An active dimethyl sulfoxide (DMSO) oxidization method is employed for the oxidization in Step ii-2. DMSO is an oxidizing agent and can be used in combination with an activating agent such as dicyclohexylcarbodiimide, phosphorus pentoxide, pyridine•sulfur trioxide complex, oxalyl chloride, acetic anhydride, and trifluoroacetic anhydride. It is preferable that the oxidization agent be employed in an amount of 1 to 4 equivalents to the alcohol derivative of formula (IB-3).

It is preferable that the above reaction in Step II-2 be carried out in a solvent. As the solvent, halogenated hydrocarbons such as dichloromethane, dichloroethane, and chloroform can be employed. Alternatively, DMSO employed as the oxidization agent can be used as the solvent for this reaction by using the same in an excessive amount. The above reaction in Step II-2 can be carried out at -20°C to 30°C.

Aldehyde derivatives (III) of the present invention, which are represented by the previously mentioned formula (II) can be prepared in accordance with the following reaction scheme:



wherein R^7 represents an aromatic hydrocarbon group, a heterocyclic group, an alkyl group having 1 to 10 carbon atoms with a substituent, or a cyclic alkyl group having 3 to 6 carbon atoms; R^8 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group; R^9 represents hydrogen, or an alkyl group having 1 to 10 carbon atoms; R^{10} represents an alkoxycarbonyl group, an acyl group, a carbamoyl group, or a sulfonyl group; X represents oxygen, or a group represented by $-S(O)_m-$ in which m is 0, 1 or 2; and n is an integer of 1 to 5.

[Step III-1]

In this step, a carboxylic acid derivative of formula (IC-1) is allowed to react with an amine derivative of formula (IC-2), whereby an ester derivative of formula (IC-3) is produced. In formula (IC-3), R^{11} represents an alkyl group having 1 to 15 carbon atoms, such as methyl group, ethyl group, propyl group, butyl group, benzyl group and diphenylmethyl group

It is preferable that the reaction in Step III-1 be carried out in the presence of a condensation agent. As the condensation agent, for instance, carbodiimide reagents such as dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC•HCl) can be employed. It is also prefer-

able that the above-mentioned condensation agent be used in an amount of 1 to 3 equivalents, more preferably in an amount of 1.5 to 2 equivalents, with respect to the carboxylic acid derivative of formula (IC-1) or the amine derivative of formula (IC-2) in order to carry out the reaction efficiently.

Furthermore, it is preferable that the above reaction in Step III-1 be carried out in an inert solvent. Examples of the inert solvent are halogenated hydrocarbons such as dichloromethane, chloroform, and dichloroethane; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, dimethoxyethane, tetrahydrofuran (THF), and dioxane; amides such as dimethylformamide; dimethyl sulfoxide (DMSO); and acetonitrile. These inert solvents can be used alone or in combination.

The reaction proceeds in the temperature range of -50°C to the reflux temperature under atmospheric pressure. However, it is preferable that the reaction temperature be set in the range of -30°C to 30°C in order to carry out the reaction efficiently.

The carboxylic acid derivatives of formula (IC-1) employed in Step III-1 are commercially available or can by obtained by converting the amino groups of commercially available amino acids to the groups of R^9 and R^{10} in formula (IC-2).

Specific examples of the carboxylic acid derivative of formula (IC-1) are as follows:

L-N-(benzyloxycarbonyl)leucine,
L-N-[1-(benzyloxycarbonyl)piperidine-4-carbonyl]leucine,
L-N-(N-phenylaminocarbonyl)leucine,
L-N-(4-methylbenzenesulfonyl)leucine,
L-N-methyl-N-(benzyloxycarbonyl)leucine,
L-N-(cinnamoyl)leucine,
L-N-(2-naphthoyl)leucine,
L-N-(benzyloxycarbonyl)valine, and
L-N-(benzyloxycarbonyl)phenylalanine.

The amine derivative of formula (IC-2) employed in Step III-2 is not only commercially available, but also can be synthesized from an amino acid represented by formula (IC-2a) in accordance with the following procedure:

$$\underset{\text{(IC-2a)}}{NH_2-\overset{\displaystyle COOH}{\overset{|}{C}H}-(CH_2)_n-X-H} \xrightarrow[R^7-X^1]{} \underset{\text{(IC-2b)}}{NH_2-\overset{\displaystyle COOH}{\overset{|}{C}H}-(CH_2)_n-X-R^7}$$

$$\xrightarrow[R^{11}-OH]{} \underset{\text{(IC-2)}}{NH_2-\overset{\displaystyle COOR^{11}}{\overset{|}{C}H}-(CH_2)_n-X-R^7}$$

wherein R^7, R^{11}, X, and n are respectively the same as defined in formula (II), and X^1 represents a halogen atom.

The amine derivative of formula (IC-2) can also be synthesized after protecting the amino group of the amino acid of formula (IC-2a) by a protective group for the amino group employed in the peptide synthesis.

Specific examples of the amine derivative of formula (IC-2) are as follows:

L-O-(benzyl)serineethyl ester,
L-S-(2-phenylethyl)cysteinemethyl ester,
L-S-(3-phenylpropyl)cysteinemethyl ester,
L-O-(3-phenylpropyl)serineethyl ester,
L-O-(3-thienylmethyl)serineethyl ester,
L-S-(diphenylmethyl)cysteinemethyl ester,
L-S-(cyclohexylmethyl)cysteineethyl ester,
L-S-(cyclopentyl)cysteineethyl ester,
L-S-(2-thienylmethyl)cysteinemethyl ester,

L-S-(3-thienylmethyl)cysteineethyl ester,
L-S-(1-naphthylmethyl)cysteineethyl ester,
L-S-(2-naphthylmethyl)cysteineethyl ester, and
L-S-(2-chlorobenzyl)cysteineethyl ester.

In Step III-1, the ester derivative of formula (IC-3) can be produced by converting the carboxyl group of the carboxylic acid derivative of formula (IC-1) to, for example, an active ester group, a carboxylic acid halide group, or an acid anhydride group to prepare an active ester compound, a carboxylic acid halide compound or an acid anhydride compound and then by allowing such a compound to react with the amine derivative of formula (IC-2) in an inert solvent in the same manner as in the previously mentioned procedure in Step III-1.

[Step III-2]

In this step, the ester derivative of formula (IC-3) is reduced to prepare the alcohol derivative of formula (IC-4).

Boron compounds such as sodium borohydride and lithium borohydride can be used as the reducing agents for the reduction in this step.

It is preferable that the amount of such a reducing agent be in the range of 1 to 4 equivalents per one mole of the ester derivative of formula (IC-3). It is also preferable that the reduction reaction be carried out in an inert solvent, for example, water, alcohols such as methanol and ethanol, ethers such as ether, THF, dimethoxyethane, and dioxane, halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane, and aromatic hydrocarbons such as benzene, toluene and xylene. These solvents can be used alone or in combination. The reduction reaction can be carried out at temperatures of -20 °C to 50 °C.

[Step III-3]

In this step, the alcohol derivative of formula (IC-4) obtained in the reaction of Step III-2 is oxidized, so that an aldehyde derivative of formula (II) is produced.

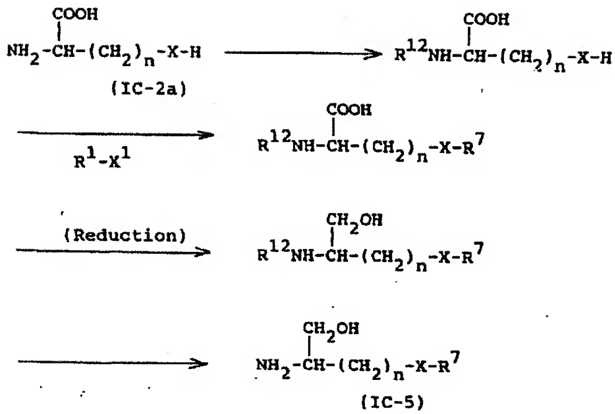
An active dimethyl sulfoxide (DMSO) oxidization method is employed for the oxidization in Step III-3. DMSO is an oxidizing agent and can be used in combination with an activating agent such as dicyclohexylcarbodiimide, phosphorus pentoxide, pyridine•sulfur trioxide complex, oxalyl chloride, acetic anhydride, and trifluoroacetic anhydride. It is preferable that the oxidization agent be employed in an amount of 1 to 4 equivalents to the alcohol derivative of formula (IC-4).

It is preferable that the above reaction in Step III-3 be carried out in a solvent, for example, halogenated hydrocarbons such as dichloromethane, dichloroethane, and chloroform, and DMSO. The above reaction in Step III-3 can be carried out at -20 °C to 30 °C.

[Step III-4]

In this step, the carboxylic acid of formula (IC-1) and the amino alcohol derivative of formula (IC-5) are allowed to react in the presence of a condensing agent to produce the alcohol derivative of formula (IC-4). This reaction can be carried out by using the same condensing agent and reaction solvent under the same conditions as in Step III-1.

The amino alcohol derivative of formula (IC-5) can be produced from the previously mentioned amino acid of formula (IC-2a) in accordance with the following reaction scheme:



wherein R^7, X, and n are respectively the same as in formula (II) and R^{12} represents a protective group for the amino group.

Specific examples of the amino alcohol derivative of formula (IC-5) are as follows:
(2R)-2-amino-3-(2-fluorobenzylthio)propanol,
(2R)-2-amino-3-(3-chlorobenzylthio)propanol,
(2R)-2-amino-3-(4-chlorobenzylthio)propanol,
(2R)-2-amino-3-(3-fluorobenzylthio)propanol,
(2R)-2-amino-3-(2-methoxybenzylthio)propanol,
(2R)-2-amino-3-(3-fluorobenzylthio)propanol,
(2R)-2-amino-3-(3-methoxybenzylthio)propanol,
(2R)-2-amino-3-(4-methoxybenzylthio)propanol,
(2R)-2-amino-3-(3-nitrobenzylthio)propanol,
(2R)-2-amino-3-(4-nitrobenzylthio)propanol,
(2S)-2-amino-4-phenoxybutanol,
(2S)-2-amino-4-(phenylthio)butanol,
(2S)-2-amino-3-(2-chlorobenzyloxy)propanol,
(2S)-2-amino-4-(2-fluorophenoxy)butanol,
(2S)-2-amino-4-(3-fluorophenoxy)butanol,
(2S)-2-amino-4-(2-chlorophenoxy)butanol,
(2S)-2-amino-4-(3-chlorophenoxy)butanol,
(2S)-2-amino-4-benzylthiobutanol,
(2S)-2-amino-4-(2-fluorobenzylthio)butanol,
(2S)-2-amino-4-(2-chlorobenzylthio)butanol,
(2S)-2-amino-4-(2-fluorophenylthio)butanol,
(2S)-2-amino-4-(2-chlorophenylthio)butanol,
(2S)-2-amino-4-(4-chlorophenylthio)butanol,
(2S)-2-amino-4-(2-chlorobenzyloxy)butanol,
(2S)-2-amino-4-(2-fluorobenzyloxy)butanol, and
(2S)-2-amino-4-(3-nitrobenzyloxy)butanol.

In this step, the carboxylic acid derivative of formula (IC-1) can be converted to an active ester compound, a carboxylic acid halide compound or an acid anhydride compound, and such a compound can be allowed to react with the amine alcohol derivative of formula (IC-5) in the same manner as in the previously mentioned procedure in Step III-1 to produce the alcohol derivative of formula (IC-4). The thus produced alcohol derivative of formula (IC-4) is oxidized by the same procedure as in Step III-3 to produce

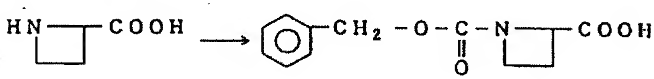
the aldehyde derivative of formula (II).

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

Other features of this invention will become apparent in the course of the following description of exemplary embodiments, which are given for illustration of the invention and are not intended to be limiting thereof.

Reference Example 1-1

Synthesis of (2R,2S)-1-benzyloxycarbonylazetidine-2-carboxylic acid (Reference Compound No. 1-1):



To 60 ml of a 1 N sodium hydroxide solution containing 5.05 g (56 mmol) of (2R,2S)-azetidine-2-carboxylic acid synthesized in accordance with the method described in Agr. Biol. Chem vol 37 (No. 3) 649 (1973), 45 ml of a 32% toluene solution of benzyloxycarbonyl chloride and 60 ml of a 1 N sodium hydroxide solution were added dropwise at the same time under an ice-cooled condition. The reaction mixture was stirred overnight at room temperature and then washed with ether twice. The reaction mixture was made acid (pH = 1 - 2) by the addition of concentrated hydrochloric acid thereto and extracted with ethyl acetate twice. The resultant organic extract layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure, whereby 9.8 g of the captioned Reference Compound No. 1-1 was obtained in a yield of 74%.

NMR (δ, $CDCl_3$): 7.30 - 7.43 (m, 5H), 5.16 (s, 2H), 4.75 - 4.90 (m, 1H), 3.90 - 4.10 (m, 2H), 2.40 - 2.65 (m, 2H)

Reference Examples 1-2 to 1-26

The same reaction procedure as in Reference Example 1-1 was repeated except that the (2R,2S)-azetidine-2-carboxylic acid and the benzyloxycarbonyl chloride used in Reference Example 1-1 were respectively replaced by Material a and Material b shown in Table 1, whereby Reference Compounds No. 1-2 to No. 1-26 were respectively obtained as shown in Table 1.

Table 1

R^2-Y-COOH (II-a)

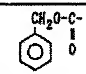
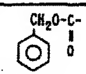
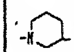
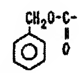
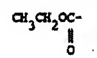
Ref. Ex.	Material a	Material b	Compound	R^2	Y	NMR(δ,$CDCl_3$)
1-2	(2R,2S)-piperidine-2-carboxylic acid	benzyloxycarbonylchloride	(2R,S)-1-benzyloxycarbonylpiperidine-2-carboxylic acid			7.25 - 7.43 (m, 5H), 5.05 - 5.20 (m, 2H), 3.90 - 4.35 (m, 2H), 2.88 - 3.25 (m, 2H), 2.45 - 2.60 (m, 1H), 2.03 - 2.15 (m, 1H), 1.40 - 1.80 (m, 3H)
1-3	(3R,3S)-piperidine-3-carboxylic acid	benzyloxycarbonylchloride	(3R,S)-1-benzyloxycarbonylpiperidine-3-carboxylic acid			7.25 - 7.45 (m, 5H), 5.17 (s, 2H), 4.85 - 5.05 (m, 1H), 4.00 - 4.19 (m, 1H), 2.93 - 3.15 (m, 1H), 2.15 - 2.35 (m, 1H), 1.20 - 1.80 (m, 5H)
1-4	piperidine-4-carboxylic acid	benzyloxycarbonylchloride	1-benzyloxycarbonylpiperidine-4-carboxylic acid			7.25 - 7.41 (m, 5H), 5.13 (s, 2H), 4.00 - 4.23 (m, 2H), 2.85 - 3.05 (m, 2H), 2.52 (tt, J=10.8Hz, 3.9Hz, 1H), 1.80 - 2.03 (m, 2H), 1.55 - 1.80 (m, 2H)
1-5	piperidine-4-carboxylic acid	ethoxycarbonylchloride	1-ethoxycarbonylpiperidine-4-carboxylic acid			4.14 (q, J=7.1Hz, 2H), 3.98 - 4.23 (m, 2H), 2.80 - 3.00 (m, 2H), 2.51 (tt, J=11.5Hz, 3.8Hz, 1H), 1.87 - 2.00 (m, 2H), 1.56 - 1.75 (m, 2H), 1.26 (t, J=7.1Hz, 3H)
1-6	piperidine-4-carboxylic acid	benzoylchloride	1-benzoylpiperidine-4-carboxylic acid			7.35 - 7.45 (m, 5H), 4.40 - 4.70 (m, 1H), 3.60 - 3.90 (m, 1H), 2.95 - 3.16 (m, 2H), 2.63 (tt, J=10.6Hz, 4.1Hz, 1H), 1.60 - 2.15 (m, 4H)

Table 1

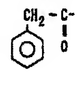
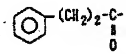
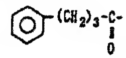
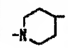
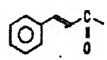
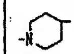
Ref. Ex.	Material a	Material b	Compound	R^2	Y	NMR(δ, $CDCl_3$)
1-7	piperidine-4-carboxylic acid	phenylacetyl chloride	1-phenylacetyl-piperidine-4-carboxylic acid			7.20 - 7.37 (m, 5H), 4.34 - 4.47 (m, 1H), 3.70 - 3.86 (m, 1H), 3.75 (s, 2H), 3.00 - 3.15 (m, 1H), 2.81 - 2.97 (m, 1H), 2.52 (tt, J=11.5Hz, 3.8Hz, 1H), 1.35 - 2.00 (m, 4H)
1-8	piperidine-4-carboxylic acid	3-phenyl-propionyl chloride	1-(3-phenylpropionyl)-piperidine-4-carboxylic acid			7.10 - 7.40 (m, 5H), 4.35 - 4.54 (m, 1H), 3.65 - 3.88 (m, 1H), 2.97 (t, J=8.0Hz, 2H), 2.64 (t, J=8.0Hz, 2H), 2.40 - 3.15 (m, 3H), 1.75 - 2.08 (m, 2H), 1.45 - 1.75 (m, 2H)
1-9	piperidine-4-carboxylic acid	4-phenyl-butyryl chloride	1-(4-phenylbutyryl)-piperidine-4-carboxylic acid			7.14 - 7.33 (m, 5H), 4.32 - 4.49 (m, 1H), 3.64 - 3.80 (m, 1H), 2.97 - 3.15 (m, 1H), 2.74 - 2.93 (m, 1H), 2.67 (t, J=7.5Hz, 2H), 2.56 (tt, J=11.5Hz, 3.8Hz, 1H), 2.34 (t, J=7.6Hz, 2H), 1.96 (t, J=7.6Hz, 2H), 1.85 - 2.03 (m, 2H), 1.57 - 1.73 (m, 2H)
1-10	piperidine-4-carboxylic acid	cinnamoyl chloride	1-cinnamoylpiperidine-4-carboxylic acid			(Solvent: CD_3OD) 7.59 - 7.64 (m, 2H), 7.55 (d, J=15.6 Hz, 1H), 7.32 - 7.44 (m, 3H), 7.15 (d, J=15.6Hz, 1H), 4.38 - 4.48 (m, 1H), 4.15 - 4.25 (m, 1H), 3.25 - 3.40 (m, 1H), 2.93 - 3.06 (m, 1H), 2.64 (tt, J=11.5Hz, 3.8Hz, 1H), 1.94 - 2.08 (m, 2H), 1.56 - 1.75 (m, 2H)

Table 1

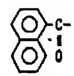
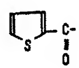
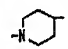
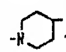
Ref. Ex.	Material a	Material b	Compound	R^2	Y	NMR(δ, $CDCl_3$)
1-11	piperidine-4-carboxylic acid	1-naphthoyl chloride	1-(1-naphthoyl)-piperidine-4-carboxylic acid			7.75 - 7.92 (m, 3H), 7.36 - 7.58 (m, 4H), 4.68 - 4.80 (m, 1H), 3.35 - 3.50 (m, 1H), 2.90 - 3.27 (m, 2H), 2.57 - 2.70 (m, 1H), 1.50 - 2.20 (m, 4H)
1-12	piperidine-4-carboxylic acid	2-naphthoyl chloride	1-(2-naphthoyl)-piperidine-4-carboxylic acid			7.80 - 8.97 (m, 4H), 7.45 - 7.65 (m, 3H), 4.40 - 4.75 (m, 1H), 3.60 - 4.00 (m, 1H), 3.00 - 3.20 (m, 2H), 2.65 (tt, J=11.5Hz, 3z8Hz, 1H), 1.60 - 2.20 (m, 4H)
1-13	piperidine-4-carboxylic acid	cyclopentanecarbonyl chloride	1-cyclopentylcarbonyl-piperidine-4-carboxylic acid			4.30 - 4.55 (m, 1H), 3.80 - 4.10 (m, 1H), 2.70 - 3.25 (m, 3H), 2.59 (tt, J=10.6Hz, 4.1Hz, 1H), 1.40 - 2.05 (m, 12H)
1-14	piperidine-4-carboxylic acid	thiophene-2-carbonyl chloride	1-(2-thienylcarbonyl)-piperidine-4-carboxylic acid			7.43 - 7.48 (m, 1H), 7.25 - 7.33 (m, 1H), 7.03 - 7.08 (m, 1H), 4.21 - 4.45 (m, 2H), 3.05 - 3.29 (m, 2H), 2.67 (tt, J=10.5Hz, 4.1Hz, 1H), 1.95 - 2.09 (m, 2H), 1.72 - 1.87 (m, 2H)
1-15	piperidine-4-carboxylic acid	trimethylacetyl chloride	1-trimethylacetyl-piperidine-4-carboxylic acid	$(CH_3)_3C-C(=O)-$		4.21 - 4.36 (m, 2H), 2.91 - 3.10 (m, 2H), 2.61 (tt, J=11.2Hz, 4.1Hz, 1H), 1.90 - 2.03 (m, 2H), 1.60 - 1.78 (m, 2H), 1.38 (s, 9H)

Table 1

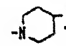
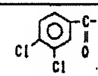
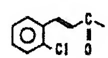
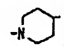
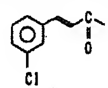
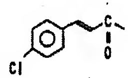
Ref. Ex.	Material a	Material b	Compound	R^2	Y	NMR(δ, $CDCl_3$)
1-16	piperidine-4-carboxylic acid	acetic anhydride	1-acetylpiperidine-4-carboxylic acid	CH_3-C(=O)-		4.34 - 4.46 (m, 1H), 3.74 - 3.87 (m, 1H), 3.10 - 3.23 (m, 1H), 2.80 - 2.93 (m, 1H), 2.59 (tt, J=11.5Hz, 3.8Hz, 1H), 2.12 (s, 3H), 1.91 - 2.05 (m, 2H), 1.59 - 1.80 (m, 2H)
1-17	piperidine-4-carboxylic acid	3,4-dichlorobenzoyl chloride	1-(3,4-dichlorobenzoyl)piperidine-4-carboxylic acid			7.45 - 7.55 (m, 2H), 7.20 - 7.29 (m, 1H), 3.40 - 4.70 (m, 2H), 2.90 - 3.25 (m, 2H), 2.64 (tt, J=10.9Hz, 4.1Hz, 1H), 1.50 - 2.20 (m, 4H)
1-18	piperidine-4-carboxylic acid	2-chlorocinnamoyl chloride	1-(2-chlorocinnamoyl)-piperidine-4-carboxylic acid			7.98 (d, J=15.5Hz, 1H), 7.20 - 7.63 (m, 4H), 6.86 (d, J=15.5Hz, 1H), 4.35 - 4.60 (m, 1H), 3.95 - 4.15 (m, 1H), 2.85 - 3.38 (m, 2H), 2.67 (tt, J=11.5Hz, 3.8Hz, 1H), 1.20 - 2.10 (m, 4H)
1-19	piperidine-4-carboxylic acid	3-chlorocinnamoyl-chloride	1-(3-chlorocinnamoyl)-piperidine-4-carboxylic acid			7.60 (d, J=15.5Hz, 1H), 7.52 (s, 1H), 7.23 - 7.43 (m, 3H), 6.88 (d, J=15.4Hz, 1H), 4.35 - 4.60 (m, 1H), 3.90 - 4.20 (m, 1H), 2.90 - 3.42 (m, 2H), 2.67 (tt, J=11.5Hz, 3.8Hz, 1H), 1.97 - 2.12 (m, 2H), 1.68 - 1.88 (m, 2H)
1-20	piperidine-4-carboxylic acid	4-chlorocinnamoyl chloride	1-(4-chlorocinnamoyl)-piperidine-4-carboxylic acid			7.62 (d, J=15.4Hz, 1H), 7.41 - 7.50 (m, 2H), 7.30 - 7.40 (m, 2H), 6.85 (d, J=15.4Hz, 1H), 4.35 - 4.62 (m, 1H), 3.90 - 4.15 (m, 1H), 2.90 - 3.40 (m, 2H), 2.65 (tt, J=11.5Hz, 3.8Hz, 1H), 1.95 - 2.10 (m, 2H), 1.68 - 1.85 (m, 2H)

Table 1

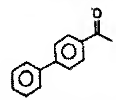
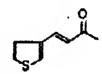
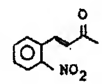
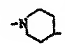
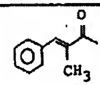
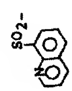
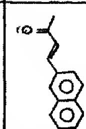
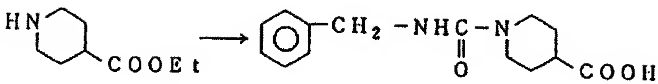
Ref. Ex.	Material a	Material b	Compound	R^2	Y	NMR(δ, $CDCl_3$)
1-21	piperidine-4-carboxylic acid	4-phenylbenzoyl chloride	1-(4-phenylbenzoyl)-piperidine-4-carboxylic acid			(Solvent: CD_3OD) 7.60 - 7.80 (m, 4H), 7.30 - 7.55 (m, 5H), 4.40 - 4.60 (m, 1H), 3.70 - 3.90 (m, 1H), 3.00 - 3.40 (m, 2H), 2.65 (tt, J=10Hz, 4Hz, 1H), 1.60 - 2.15 (m, 4H)
1-22	piperidine-4-carboxylic acid	3-(3-thienyl)-acrylic acid chloride	1-[3-(3-thienyl)-acryloyl]piperidine-4-carboxylic acid			(Solvent: CD_3OD) 7.70 (d, J=15Hz, 1H), 7.48 (d, J=5Hz, 1H), 7.34 (d, J=3Hz, 1H), 7.07 (dd, J=5Hz, 3Hz, 1H), 6.90 (d, J=15Hz, 1H), 4.35 - 4.50 (m, 1H), 4.05 - 4.25 (m, 1H), 3.20 - 3.40 (m, 1H), 2.90 - 3.10 (m, 1H), 2.63 (tt, J=10Hz, 4Hz, 1H), 1.90 - 2.10 (m, 2H), 1.50 - 1.80 (m, 2H)
1-23	piperidine-4-carboxylic acid	2-nitrocinnamoyl chloride	1-(2-nitrocinnamoyl)-piperidine-4-carboxylic acid			(Solvent: CD_3OD) 8.01 (d, J=9Hz, 1H), 7.85 - 7.95 (m, 2H), 7.71 (t, J=7Hz, 1H), 7.59 (t, J=9Hz, 1H), 7.11 (d, J=15Hz, 1H), 4.35 - 4.50 (m, 1H), 4.15 - 4.25 (m, 1H), 4.25 - 4.40 (m, 1H), 2.95 - 3.10 (m, 1H), 2.65 (tt, J=10Hz, 4Hz, 1H), 1.95 - 2.10 (m, 2H), 1.60 - 1.80 (m, 2H)
1-24	piperidine-4-carboxylic acid	3-phenyl-2-methyl-acrylic acid chloride	1-[(3-phenyl-2-methyl)acryloyl]-piperidine-4-carboxylic acid			7.20 - 7.40 (m, 5H), 6.52 (s, 1H), 3.70 - 4.60 (m, 2H), 2.90 - 3.30 (m, 2H), 2.62 (tt, J=11Hz, 4Hz, 1H), 2.09 (s, 3H), 1.90 - 2.10 (m, 2H), 1.65 - 1.80 (m, 2H)

Table 1

1-25	piperidine-4-carboxylic acid	quinoline-8-sulfonyl chloride	1-(8-quinolylsulfonyl)-piperidine-4-carboxylic acid			(Solvent: CD_3OD) 9.03 (d, J=4Hz, 1H), 8.40 - 8.50 (m, 2H), 8.20 (d, J=7Hz, 1H), 7.04 (t, J=8Hz, 1H), 7.62 (dd, J=8Hz, 4Hz, 1H), 3.85 - 4.00 (m, 2H), 2.85 - 3.00 (m, 2H), 2.34 (tt, J=10Hz, 4Hz, 1H), 1.85 - 2.00 (m, 2H), 1.55 - 1.70 (m, 2H)
1-26	piperidine-4-carboxylic acid	3-(2-naphthyl)-acrylic acid chloride	1-[3-(2-naphthyl)-acryloyl]piperidine-4-carboxylic acid			8.20 - 9.50 (m, 1H), 7.35 - 8.00 (m, 8H), 6.98 (d, J=15Hz, 1H), 3.80 - 4.75 (m, 2H), 2.80 - 3.50 (m, 2H), 2.65 (tt, J=10Hz, J=4Hz, 1H), 1.92 - 2.14 (m, 2H), 1.65 - 1.90 (m, 2H)

Reference Example 1-27

Synthesis of 1-(N-benzylcarbamoyl)piperidine-4-carboxylic acid (Reference Compound No. 1-27):



Under an ice-cooled condition, 28.9 ml (0.398 mol) of thionyl chloride was added dropwise to 200 ml of an ethanol suspension containing 25 g (0.193 mol) of piperidine-4-carboxylic acid. The reaction mixture was stirred at room temperature for 18 hours, and then concentrated under reduced pressure. The residue thus obtained was dissolved in ethanol. With the addition of ether to this reaction mixture, crystals separated out. These crystals were separated by filtration and dried, so that 36.3 g of piperidine-4-carboxylic acid ethyl ester hydrochloride was obtained in a yield of 97%. To a methylene chloride suspension containing 7.28 g (37.6 mmol) of the above prepared ester hydrochloride, 10.5 ml (75.2 mmol) of triethylamine and benzyl isocyanate were successively added under an ice-cooled condition. The reaction mixture was then stirred overnight at room temperature. The reaction mixture was washed successively with 1 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure, whereby 7.58 g of 1-(N-benzylcarbamoyl)piperidine-4-carboxylic acid ethyl ester was obtained in a yield of 68%.

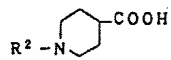
53 ml of a 1 N sodium hydroxide solution was added to 50 ml of a methanol solution containing 7 g (24.1 mmol) of the above prepared ethyl ester under an ice-cooled condition. The reaction mixture was stirred for 3 hours, and then concentrated under reduced pressure. The residue thus obtained was dissolved in water and washed with ether twice. The resulting water layer was made acid (pH=1) by the addition of concentrated hydrochloric acid thereto. The water layer was extracted with chloroform twice and dried over anhydrous sulfate. The solvent was distilled away under reduced pressure, whereby 5.94 g of the captioned Reference Compound No. 1-27 was obtained in a yield of 94%.

NMR (δ, CD_3OD): 7.17 - 7.38 (m, 5H), 4.35 (s, 2H), 3.87 - 4.05 (m, 2H), 2.84 - 3.04 (m, 2H), 2.52 (tt, J=11.0Hz, 4.0Hz, 1H), 1.80 - 1.99 (m, 2H), 1.45 - 1.83 (m, 2H)

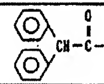
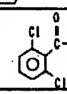
Reference Examples 1-28 to 1-32

The same reaction procedure as in Reference Example 1-27 was repeated except that benzyl isocyanate used in Reference Example 1-27 was replaced by the respective materials shown in Table 2, whereby Reference Compounds No. 1-28 to No. 1-32 were respectively obtained as shown in Table 2.

Table 2

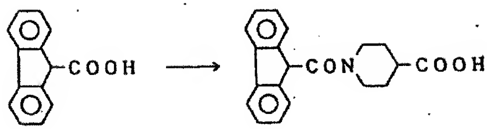


(II-b)

Ref. Ex.	Material	Compound	R^2	NMR(δ,$CDCl_3$)
1-28	phenyl isocyanate	1-(N-phenylcarbamoyl)-piperidine-4-carboxylic acid		(Solvent: CD_3OD) 7.20 - 7.37 (m, 4H), 6.97 - 7.04 (m, 1H), 4.02 - 4.15 (m, 2H), 2.95 - 3.10 (m, 2H), 2.57 (tt, J=10.9Hz, 4.0Hz, 1H), 1.90 - 2.02 (m, 2H), 1.58 - 1.75 (m, 2H)
1-29	4-methylbenzenesulfonyl chloride	1-(4-methylphenyl-sulfonyl)piperidine-4-carboxylic acid		7.64 (d, J=8.3Hz, 2H), 7.33 (d, J=7.9Hz, 2H), 3.60 - 3.70 (m, 2H), 2.44 (s, 3H), 2.40 - 2.53 (m, 2H), 2.29 (tt, J=10.7Hz, 4.0Hz, 1H), 1.75 - 2.05 (m, 4H)
1-30	naphthalene-2-sulfonyl chloride	1-(2-naphthyl-sulfonyl)piperidine-4-carboxylic acid		8.33 (s, 1H), 7.88 - 8.03 (m, 3H), 7.57 - 7.78 (m, 3H), 3.62 - 3.78 (m, 2H), 2.45 - 2.62 (m, 2H), 2.20 - 2.34 (m, 1H), 1.75 - 2.10 (m, 4H)
1-31	diphenylacetyl chloride	1-diphenylacetyl-piperidine-4-carboxylic acid		7.23 - 7.38 (m, 10H), 5.20 (s, 1H), 4.35 - 4.54 (m, 1H), 3.75 - 3.95 (m, 1H), 2.80 - 3.15 (m, 2H), 2.50 (tt, J=11.2Hz, 3.9Hz, 1H), 1.20 - 2.05 (m, 4H)
1-32	2,6-dichlorobenzoyl chloride	1-(2,6-dichloro-benzoyl)piperidine-4-carboxylic acid		7.20 - 7.37 (m, 3H), 4.50 - 4.62 (m, 1H), 3.35 - 3.49 (m, 1H), 3.05 - 3.25 (m, 2H), 2.63 (tt, J=11.0Hz, 4.0Hz, 1H), 1.71 - 2.19 (m, 4H)

Reference Example 1-33

Synthesis of 1-(9-fluorenylcarbonyl)piperidine-4-carboxylic acid (Reference Compound No. 1-33):



To 100 ml of a tetrahydrofuran solution of 5 g (23.8 mmol) of 9-fluorene carboxylic acid, 2.74 g (23.8 mmol) of N-hydroxysuccinimide and 5.40 g (26.2 mmol) of N,N'-dicyclohexyl carbodiimide were successively added under an ice-cooled condition. After stirring the above mixture for 3 hours, dicyclohexylurea was removed from the reaction mixture by filtration. To the filtrate, 4.61 g (23.8 mmol) of piperidine-4-carboxylic acid ethyl ester hydrochloride and 3.33 ml (23.8 mmol) of triethylamine were added at -0 °C. The reaction mixture was further stirred overnight at room temperature. The solvent was distilled away from the reaction mixture under reduced pressure. Ethyl acetate was added to the residue and the mixture was washed successively with a 1 N hydrochloric acid solution, a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 6.10 g of ethyl 1-(9-fluorenylcarbonyl)piperidine-4-carboxylate was obtained in a yield of 73%.

6.10 g (17.5 mmol) of the above prepared ethyl 9-fluorenylcarbonylpiperidine-4-carboxylate was dissolved in 35 ml of methanol. With the addition of 38.5 ml of a 1 N sodium hydroxide solution under an ice-cooled condition, the reaction mixture was stirred for one hour. Subsequently, a 1 N hydrochloric acid solution was added to the reaction mixture until it became neutral, and then the methanol was distilled away from the reaction mixture under reduced pressure. The residue thus obtained was made basic with the addition of a 1 N sodium hydroxide solution and washed with ether. The resultant water layer was made acid (pH=1) by the addition of 4 N hydrochloric acid, and extracted with ethyl acetate. The extract layer was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 5.75 g of the captioned Reference compound No. 1-33 was obtained.

NMR (δ, $CDCl_3$): 7.80 (d, 7.3Hz, 2H), 7.28 - 7.70 (m, 6H), 5.06 (s, 1H), 4.25 - 4.45 (m, 1H), 0.60 - 3.15 (m, 8H)

Reference Examples 1-34 to 1-41

The same procedure as in Reference Example 1-33 was repeated except that the 9-fluorene carboxylic acid used in Example 1-33 was replaced by the respective carboxylic acids shown in Table 3, whereby Reference Compounds No. 1-34 to No. 1-41 were respectively obtained as shown in Table 3.

Table 3

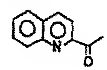
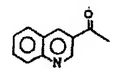
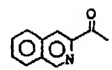
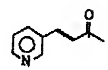
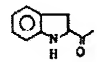
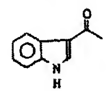
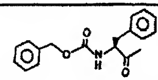
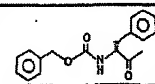
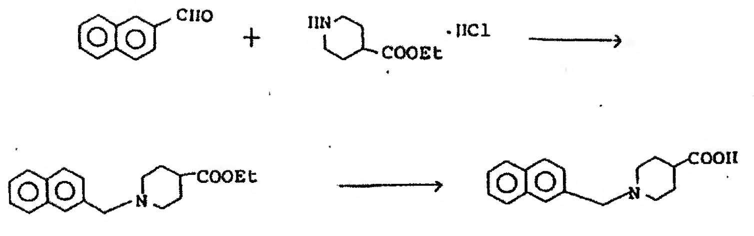
Ref. Ex.	Material	Compound	R^2	NMR(δ, $CDCl_3$)
1-34	quinoline-2-carboxylic acid	1-(2-quinolyl-carbonyl)piperidine-4-carboxylic acid		8.28 (d, J=8Hz, 1H), 8.15 (d, J=8Hz, 1H), 7.86 (d, J=8Hz, 1H), 7.76 (t, J=7Hz, 1H), 7.68 (d, J=8Hz, 1H), 7.61 (t, J=7Hz, 1H), 4.55 - 4.70 (m, 1H), 3.90 - 4.05 (m, 1H), 3.10 - 3.30 (m, 2H), 2.30 - 2.45 (m, 1H), 1.80 - 2.20 (m, 4H)
1-35	quinoline-3-carboxylic acid	1-(3-quinolyl-carbonyl)piperidine-4-carboxylic acid		(Solvent: CD_3OD) 8.89 (d, J=2Hz, 1H), 8.44 (d, J=2Hz, 1H), 8.08 (d, J=8Hz, 1H), 8.04 (d, J=8Hz, 1H), 7.85 - 7.95 (m, 1H), 7.65 - 7.75 (m, 1H), 4.45 - 4.60 (m, 1H), 3.70 - 3.90 (m, 1H), 3.10 - 3.40 (m, 2H), 2.67 (tt, J=10Hz, 4Hz, 1H), 1.65 - 2.20 (m, 4H)
1-36	isoquinoline-3-carboxylic acid	1-(3-isoquinolyl-carbonyl)piperidine-4-carboxylic acid		9.36 (s, 1H), 8.06 (d, J=8Hz, 1H), 8.02 (s, 1H), 7.92 (d, J=8Hz, 1H), 7.79 (t, J=8Hz, 1H), 7.70 (t, J=8Hz, 1H), 4.50 - 4.70 (m, 1H), 3.70 - 3.90 (m, 1H), 3.00 - 3.30 (m, 4H), 2.55 - 2.70 (m, 1H), 1.80 - 2.20 (m, 4H)
1-37	3-(2-pyridyl)acrylic acid	1-[3-(2-pyridyl)-acryloyl]piperidine-4-carboxylic acid		(Solvent: CD_3OD) 8.76 (d, J=2Hz, 1H), 8.50 (dd, J=5Hz, 2Hz, 1H), 8.15 (d, t, J=8Hz, 2Hz, 1H), 7.57 (d, J=15Hz, 1H), 7.47 (dd, J=8Hz, 5Hz, 1H), 7.33 (d, J=15Hz, 1H), 4.40 - 4.50 (m, 1H) 4.15 - 4.30 (m, 1H), 3.25 - 3.40 (m, 1H), 2.90 - 3.10 (m, 1H), 2.65 (tt, J=10Hz, 4Hz, 1H), 1.95 - 2.10 (m, 2H), 1.55 - 1.80 (m, 2H)

Table 3

Ref. Ex.	Material	Compound	R^2	NMR(δ, $CDCl_3$)
1-38	indole-2-carboxylic acid	1-(2-indolylcarbonyl)-piperidine-4-carboxylic acid		(Solvent: CD_3OD) 7.61 (d, J=8Hz, 1H), 7.42 (d, J=8Hz, 1H), 7.20 (td, J=8Hz, J=1Hz, 1H), 7.06 (td, J=8Hz, J=1Hz, 1H), 6.79 (s, 1H), 4.38 - 4.52 (m, 2H), 3.10 - 3.48 (m, 2H), 2.68 (tt, J=11Hz, J=4Hz, 1H), 1.97 - 2.12 (m, 2H), 1.66 - 1.85 (m, 2H)
1-39	indole-3-carboxylic acid	1-(3-indolylcarbonyl)-piperidine-4-carboxylic acid		(Solvent: CD_3OD) 7.62 (td, J=7Hz, J=2Hz, 1H), 7.60 (s, 1H), 7.44 (dd, J=7Hz, J=2Hz, 1H), 7.17 (m, 2H), 4.21 - 4.42 (m, 2H), 3.12 - 3.32 (m, 2H), 2.64 (tt, J=10Hz, J=4Hz, 1H), 1.60 - 2.05 (m, 4H)
1-40	L-N-(benzyloxycarbonyl)-phenylalanine	1-(N-benzyloxy-carbonyl-L-phenyl-alanyl)piperidine-4-carboxylic acid		7.07 - 7.42 (m, 10H), 5.85 - 5.98 (m, 1H), 4.80 - 5.16 (m, 3H), 4.15 - 4.40 (m, 1H), 3.50 - 3.70 (m, 1H), 2.30 - 3.10 (m, 5H), 0.60 - 1.95 (m, 4H)
1-41	D-N-(benzyloxycarbonyl)-phenylalanine	1-(N-benzyloxy-carbonyl-D-phenyl-alanyl)piperidine-4-carboxylic acid		7.05 - 7.45 (m, 10H), 5.87 - 6.02 (m, 1H), 4.80 - 5.18 (m, 3H), 4.17 - 4.41 (m, 1H), 3.50 - 3.72 (m, 1H), 2.30 - 3.12 (m, 5H), 0.40 - 1.95 (m, 4H)

Reference Example 1-42

Synthesis of 1-(2-naphthylmethyl)piperidine-4-carboxylic acid (Reference Compound No. 1-42):



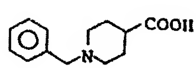
2.17 ml (15.5 mmol) of triethylamine, 4.84 g (31.0 mmol) of 2-naphthoaldehyde and 0.3 g of a 10% palladium carbon were added to an ethanol solution containing 3.0 g (15.5 mmol) of piperidine-4-carboxylic acid ethyl ester hydrochloride. The above prepared reaction mixture was stirred overnight in a stream of hydrogen gas and the palladium carbon was separated therefrom by filtration. The solvent was distilled away under reduced pressure. The residue thus obtained was dissolved in 1 N hydrochloric acid and washed with ether. The resultant water layer was made basic with the addition of sodium hydrogencarbonate and extracted with dichloromethane. The resultant extract organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 4.05 g of N-(2-naphthylmethyl)piperidine-4-carboxylic acid ethyl ester was obtained in a yield of 88%.

4.05 g (13.6 mmol) of the above prepared ester was dissolved in methanol. With the addition of 30 ml (30 mmol) of 1 N sodium hydroxide aqueous solution, the reaction mixture was stirred. The pH of the reaction mixture was adjusted to 7.0 with the addition of 4 N hydrochloric acid. The solvent was distilled away from the reaction mixture under reduced pressure. The residue thus obtained was dissolved in 1 N sodium hydroxide and washed with ether. The pH of the resulting water layer was adjusted to 2 with the addition of 4 N hydrochloric acid and extracted with a mixed solvent of chloroform and 2-butanol. The resultant extract organic layer was dried over anhydrous sodium sulfate and the solvent was distilled away under reduced pressure, whereby 3.70 g of N-(2-naphthyl-methyl)piperidine-4-carboxylic acid was obtained in a yield of 100%.

NMR (δ, CD_3OD): 7.90 - 8.08 (m, 4H), 7.54 - 7.63 (m, 3H), 4.46 (s, 2H), 3.40 - 3.55 (m, 2H), 3.05 - 3.27 (m, 2H), 2.55 - 2.71 (m, 1H), 1.82 - 2.25 (m, 4H)

Reference Example 1-43

Synthesis of 1-benzyl-piperidine-4-carboxylic acid (Reference Compound No. 1-43):

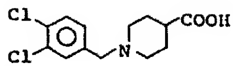


The same procedure as in Reference Example 1-42 was repeated except that the 4.84 g (31.0 mmol) of 2-naphthoaldehyde used in Reference Example 1-42 was replaced by 5.24 ml (31.6 mmol) of benzaldehyde, whereby the captioned Reference Compound No. 1-43 was obtained.

NMR (δ, CD_3OD): 7.40 - 7.65 (m, 5H), 4.33 (s, 2H), 2.90 - 3.65 (m, 4H), 2.50 - 2.80 (m, 1H), 1.70 - 2.40 (m, 4H)

Reference Example 1-44

Synthesis of 1-(3,4-dichlorobenzyl)-piperidine-4-carboxylic acid (Reference Compound No. 1-44):

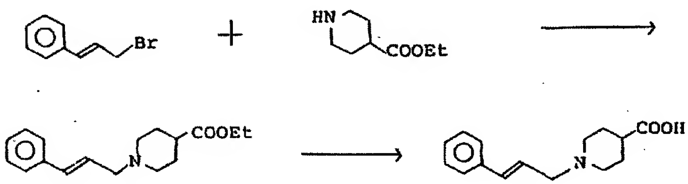


The same procedure as in Reference Example 1-42 was repeated except that the 4.84 g (31.0 mmol) of 2-naphthoaldehyde used in Reference Example 1-42 was replaced by 4.10 g (23.4 mmol) of 3,4-dichlorobenzaldehyde, whereby the captioned Reference Compound No. 1-44 was obtained.

NMR (δ, CD_3OD): 7.62 (d, J=2Hz, 1H), 7.55 (d, J=8Hz, 1H), 7.41 (dd, J=8Hz, J=2Hz, 1H), 3.84 (s, 2H), 3.02 - 3.15 (m, 2H), 2.45 - 2.62 (m, 2H), 2.34 (tt, J=10Hz, J=4Hz, 1H), 1.72 - 2.10 (m, 4H)

Reference Example 1-45

Synthesis of 1-cinnamylpiperidine-4-carboxylic acid (Reference Compound No. 1-45):



3.53 g (25.7 mmol) of potassium carbonate and 3.80 ml (25.7 mmol) of cinnamyl bromide were added to an acetonitrile solution containing 4.04 g (25.7 mmol) of piperidine-4-carboxylic acid ethyl ester. The above prepared reaction mixture was refluxed for 4 hours and the solvent was distilled away therefrom under reduced pressure. The residue thus obtained was dissolved in chloroform and washed successively with a saturated aqueous solution of sodium chloride containing 5% citric acid, a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride. The resultant extract organic layer was dried over anhydrous sodium sulfate and the solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 3.97 g of N-cinnamyl-piperidine-4-carboxylic acid ethyl ester was obtained in a yield of 57%.

3.97 g (14.5 mmol) of the above prepared ester was dissolved in methanol and 32 ml (32 mmol) of a 1 N sodium hydroxide aqueous solution was added to the reaction mixture, followed by stirring for 3 hours. The pH of reaction mixture was adjusted to 7 with the addition of 4 N hydrochloric acid and the solvent was distilled away therefrom under reduced pressure. The residue thus obtained was dissolved in 1 N sodium hydroxide and washed with ether. The pH of the resulting water layer was adjusted to 2 with the addition of 4 N hydrochloric acid and extracted with a mixed solvent containing chloroform and 2-butanol. The resultant extract organic layer was dried over anhydrous sodium sulfate and the solvent was distilled away under reduced pressure, whereby 3.25 g of the captioned Reference Compound No. 1-45 was obtained in a yield of 91%.

NMR (δ, CD_3OD): 7.25 - 7.60 (m, 5H), 6.91 (d, J=16Hz, 1H), 6.34 (dt, J=16Hz, J=7Hz, 1H), 3.89 (d, J=7Hz, 2H), 3.40 - 3.65 (m, 2H), 2.95 - 3.25 (m, 2H), 2.55 - 2.75 (m, 1H), 1.80 - 2.32 (m, 4H)

Reference Example 1-46

Synthesis of (2S)-2-amino-4-methylthiobutanol (Reference Compound No. 1-46):

38 ml (300 mmol) of chlorotrimethylsilane was added dropwise to 200 ml of an anhydrous tetrahydrofuran suspension containing 3.3 g (150 mmol) of lithium borohydride under an ice-cooled condition. The reaction mixture was stirred for 30 minutes. 7.5 g (50 mmol) of L-methionine was gradually added to the reaction mixture, followed by stirring overnight at room temperature. Methanol was further added to the reaction mixture under an ice-cooled condition until the evolution of hydrogen gas ceased. The solvent was distilled away from the reaction mixture under reduced pressure. A 10% sodium hydroxide solution was added to the thus obtained residue, followed by the extraction with chloroform twice. After the resultant chloroform extract layer was dried over anhydrous sodium sulfate, the solvent was distilled away under reduced pressure, whereby 5.12 g of the captioned Reference Compound No. 1-46 was obtained in a yield of 75%.

NMR (δ, $CDCl_3$): 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.33 (dd, J=11Hz, J=7Hz, 1H), 2.98 - 3.04 (m, 1H), 2.57 - 2.64 (m, 2H), 2.22 - 2.43 (m, 3H), 2.11 (s, 3H), 1.68 - 1.80 (m, 1H), 1.50 - 1.62 (m, 1H)

Reference Examples 1-47 to 1-53

The same reaction procedure in Reference Example 1-46 was repeated except that the L-methionine used in Reference Example 1-46 was replaced by the material shown in Table 4, whereby Reference Compounds No. 1-47 to No. 1-53 were respectively obtained as shown in Table 4.

Table 4

$$H_2N\text{-}\underset{}{\overset{CH_2OH}{\overset{|}{C}H}}\text{-}(CH_2)n\text{-}R^1 \quad \text{(III-a)}$$

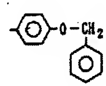
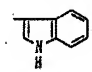
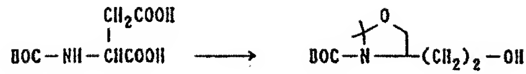
Ref. Ex.	Material	Compound	n	R^1	NMR(δ, $CDCl_3$)
1-47	L-leucine	(2S)-2-amino-4-methyl-pentanol	1	$-CH(CH_3)CH_3$	3.63 (dd, J=11Hz, 3Hz, 1H), 3.48 (dd, J=11Hz, 1H), 2.60 - 2.80 (m, 1H), 2.05 (brs, 3H), 2.50 - 2.70 (m, 1H), 1.30 - 1.45 (m, 2H), 0.83 - 1.05 (m, 6H)
1-48	L-phenylalanine	(2S)-2-amino-3-phenyl-propanol	1		7.16 - 7.33 (m, 5H), 3.64 (dd, J=11Hz, J=4Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 3.07 - 3.16 (m, 1H), 2.79 (dd, J=14Hz, J=5Hz, 1H), 2.52 (dd, J=14Hz, J=9Hz, 1H), 2.10 (brs, 3H)
1-49	L-tyrosine-o-benzylether	(2S)-2-amino-4-(4-benzyl-oxyphenyl)propanol	1		7.27 - 7.47 (m, 5H), 7.10 (d, J=8.6Hz, 2H), 6.92 (d, J=8.6Hz, 2H), 5.05 (s, 2H), 3.63 (dd, J=10.6Hz, J=3.9Hz, 1H), 3.37 (dd, J=10.6Hz, J=7.2Hz, 1H), 3.02 - 3.13 (m, 1H) 2.73 (dd, J=13.6Hz, J=5.3Hz, 1H), 2.47 (dd, J=13.7Hz, J=8.6Hz, 1H), 1.70 - 1.95 (m, 3H)
1-50	L-homophenyl-alanine	(2S)-2-amino-4-phenyl-butanol	2		7.17 - 7.31 (m, 5H), 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.31 (dd, J=11Hz, J=8Hz, 1H), 2.80 - 2.88 (m, 1H), 2.60 - 2.79 (m, 2H), 1.95 (brs, 3H), 1.70 - 1.80 (m, 1H), 1.52 - 1.64 (m, 1H)
1-51	L-norleucine	(2S)-2-aminohexanol	3	$-CH_3$	3.58 (dd, J=10Hz, 3Hz, 1H), 3.27 (dd, J=10Hz, 8Hz, 1H), 2.75 - 2.90 (m, 1H), 2.13 (brs, 3H), 1.20 - 1.50 (m, 6H), 0.80 - 1.00 (m, 3H)

Table 4

Ref. Ex.	Material	Compound	n	R^1	NMR(δ, $CDCl_3$)
1-52	L-tryptophan	(2S)-2-amino-3-(3-indolyl)-propanol	1		(Solvent: CD_3OD) 7.56 (d, J=7Hz, 1H), 7.34 (d, J=7Hz, 1H), 6.90 - 7.15 (m, 3H), 3.58 (dd, J=10Hz, 4Hz, 1H), 3.39 (dd, J=10Hz, 7Hz, 1H), 3.05 - 3.20 (m, 1H), 2.90 (dd, J=14Hz, 6Hz, 1H), 2.69 (dd, J=14Hz, 7Hz, 1H)
1-53	L-o-fluoro-phenylalanine	(2S)-2-amino-3-(2-fluoro-phenyl)propanol	1		6.90 - 7.30 (m, 4H), 3.66 (dd, J=10Hz, 4Hz, 1H), 3.78 (dd, J=10Hz, 7Hz, 1H), 3.05 - 3.20 (m, 1H), 2.81 (dd, J=13Hz, 5Hz, 1H), 2.63 (dd, J=13Hz, 8Hz, 1H), 2.02 (brs, 3H)

Reference Example 1-54

Synthesis of (4S)-2,2-dimethyl-3-(t-butoxycarbonyl)-4-(2-hydroxyethyl)-1,3-oxazolidine (Reference Compound No. 1-54):



40.1 g (0.4 mol) of potassium hydrogencarbonate was added to an anhydrous N,N'-dimethylformamide solution containing 23.4 g (0.1 mol) of t-butoxycarbonyl-L-aspartic acid. The above mixture was stirred at room temperature for one hour. Furthermore, the reaction mixture was stirred overnight at room temperature after the dropwise addition of 31.1 ml (0.5 mol) of methyl iodide. Water was then added to the reaction mixture, followed by the extraction with ethyl acetate. The resultant organic extract layer was successively washed with 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 25.8 g of a dimethyl ester was obtained in a yield of 99%.

A tetrahydrofuran solution containing 25.7 g (98.4 mmol) of the above prepared dimethyl ester was added to a tetrahydrofuran solution containing 4.3 g (196.8 mmol) of lithium borohydride. To this reaction mixture, 50 ml of methanol was further added dropwise. After stirring for two hours, water was added to the reaction mixture and the solvent was distilled away therefrom under reduced pressure. To the residue thus obtained, 1 N hydrochloric acid was added. The mixture was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 18.5 g of a diol was obtained in a yield of 92%.

83 ml (675 mmol) of 2,2-dimethoxypropane and 1.28 g (6.75 mmol) of p-toluene sulfonic acid hydrate were added to a methylene chloride solution containing 27.6 g (135 mmol) of the above prepared diol. The reaction mixture was stirred overnight at room temperature. The reaction mixture was washed with a saturated solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The thus obtained residue was chromatographed on a silica gel column for purification, whereby 19.9 g of the captioned Reference Compound No. 1-54 was obtained in a yield of 60%.

NMR (δ, $CDCl_3$): 4.18 - 4.27 (m, 1H), 3.99 - 4.04 (m, 1H), 3.50 - 3.71 (m, 3H), 2.70 - 3.00 (brs, 1H), 1.70 - 1.90 (m, 2H), 1.55 (s, 6H), 1.50 (s, 9H)

Reference Example 1-55

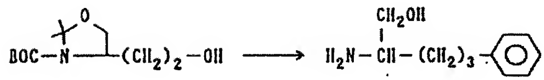
Synthesis of (4S)-2,2-dimethyl-3-(t-butoxycarbonyl)-4-(3-hydroxypropyl)-1,3-oxazolidine (Reference Compound No. 1-55):

The reaction procedure in Reference Example 1-54 was repeated except that the t-butoxycarbonyl-L-aspartic acid used in Reference Example 1-54 was replaced by the t-butoxycarbonyl-L-glutamic acid, whereby the captioned Reference Compound No. 1-55 was obtained.

NMR (δ, $CDCl_3$): 3.55 - 4.02 (m, 5H), 2.19 (s, 1H), 1.35 - 2.00 (m, 19H)

Reference Example 1-56

Synthesis of (2S)-2-amino-5-phenylpentanol (Reference Compound No. 1-56):



A methylene chloride solution containing 4.1 ml (46.8 mmol) of oxalyl chloride was cooled to -78°C. To this solution, 6.84 ml (97.2 mmol) of dimethyl sulfoxide was added dropwise with stirring. After one hour, a methylene chloride solution containing 9.82 g (40 mmol) of the Reference Compound No. 1-54 synthesized in Reference Example 1-54 was added to the above solution. This reaction solution was further stirred for 3 hours, followed by addition of 27.9 ml (200 mmol) of triethylamine. The reaction mixture was further stirred for 30 minutes. After the temperature of the reaction mixture was raised to room temperature, the reaction mixture was poured into water to separate an organic layer therefrom. The remaining water layer was extracted with methylene chloride, and a mixture of the thus obtained extract layer and the organic layer was washed successively with a 1 N hydrochloric acid solution and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 7.15 g of (4S)-2,2-dimethyl-3-(t-butoxycarbonyl)-4-(formylmethyl)-1,3-oxazolidine was obtained in a yield of 74%.

NMR (δ, $CDCl_3$): 9.79 (s, 1H), 4.25 - 4.40 (m, 1H), 4.04 - 4.09 (m, 1H), 3.73 (dd, J=9Hz, J=2Hz, 1H), 2.82 - 3.10 (m, 1H), 2.62 - 2.80 (m, 1H), 1.61 (s, 3H), 1.55 (m, 3H), 1.48 (s, 9H)

An anhydrous tetrahydrofuran solution containing 3.28 g (29.2 mmol) of potassium tert-butoxide was added dropwise to an anhydrous tetrahydrofuran suspension of 18.98 g (43.8 mmol) of triphenylbenzyl phosphonium bromide at -78°C with stirring. The temperature of the reaction solution was raised to room temperature over a period of one hour, and then cooled to -78°C. To this solution, an anhydrous tetrahydrofuran containing 7.10 g (29.2 mmol) of the above prepared oxazolidine aldehyde was added dropwise.

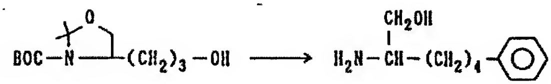
After the completion of the dropwise addition, the reaction solution was allowed to warm to room temperature, followed by stirring for one hour. With the addition of a saturated ammonium chloride solution to the above reaction solution, the solvent was distilled away therefrom under reduced pressure. A water layer was extracted with ethyl acetate. The resultant organic extract layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 7.5 g of an olefin was obtained in a yield of 82%.

To a methanol solution containing 7.5 g (23.9 mmol) of the above obtained olefin, 2.00 g of a 10% palladium carbon was added. This solution was stirred overnight at room temperature under a stream of hydrogen. The palladium carbon was removed from the solution by filtration, and then the solvent was distilled away from the filtrate under reduced pressure. To a methanol solution containing the thus obtained residue, an ethyl acetate solution containing 4 N hydrogen chloride (4 N HCl - AcOEt) was added with being cooled. The reaction mixture was stirred for one hour. The solvent was distilled away under reduced pressure and the residue thus obtained was dissolved in water and then washed with ethyl acetate. Potassium carbonate was added to the resultant water layer to make the reaction product in the water layer basic. The water layer was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 1.34 g of the captioned Reference Compound No. 1-56 was obtained in a yield of 31%.

NMR (δ, $CDCl_3$): 7.26 - 7.31 (m, 2H), 7.16 - 7.20 (m, 3H), 3.57(dd, J=11Hz, J=4Hz, 1H), 3.25 (dd, J=11Hz, J=8Hz, 1H), 2.80 - 2.88 (m, 1H), 2.60 - 2.68 (m, 2H), 1.82 - 1.90 (m, 3H), 1.60 - 1.80 (m, 2H), 1.40 - 1.50 (m, 1H), 1.24 - 1.37 (m, 1H)

Reference Example 1-57

Synthesis of (2S)-2-amino-6-phenylhexanol (Reference Compound No. 1-57):



The same reaction procedure as in Reference Example 1-56 was repeated except that the (4S)-2,2-dimethyl-3-(t-butoxycarbonyl)-4-(2-hydroxyethyl)-1,3-oxazolidine used in Reference Example 1-56 was replaced by (4S)-2,2-dimethyl-3-(t-butoxycarbonyl)-4-(3-hydroxypropyl)-1,3-oxazolidine synthesized in Reference Example 1-55, whereby the captioned Reference Compound No. 1-57 was obtained.

NMR (δ, $CDCl_3$): 7.05 - 7.25 (m, 5H), 3.50 (dd, J=10.6Hz, J=3.8Hz, 1H), 3.18 (dd, J=10.6Hz, J=7.8Hz, 1H), 2.65 - 2.80 (m, 1H), 2.55 (t, J=15.2Hz, 2H), 1.75 - 2.00 (m, 3H), 1.10 - 1.65 (m, 6H)

Reference Example 1-58

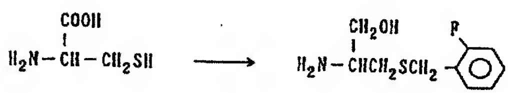
Synthesis of (2S)-2-amino-7-phenylheptanol (Reference Compound No. 1-58):

The same reaction procedure as in Reference Example 1-56 was repeated except that, the triphenylbenzyl phosphonium bromide used in Reference Example 1-56 was replaced by triphenyl(3-phenyl)-propylphosphonium bromide, whereby the captioned Reference Compound No. 1-58 was obtained.

NMR (δ, $CDCl_3$): 7.20 - 7.35 (m, 2H), 7.10 - 7.20 (m, 3H), 3.50 - 3.85 (m, 3H), 3.64 (dd, J=10Hz, 3Hz, 1H), 3.35 (dd, J=10Hz, 7Hz, 1H), 2.85 - 3.00 (m, 1H), 2.58 (t, J=7Hz, 2H), 1.50 - 1.80 (m, 2H), 1.20 - 1.55 (m, 6H)

Reference Example 1-59

Synthesis of (2R)-2-amino-3(2-fluorobenzylthio)propanol (Reference Compound No. 1-59):



6.9 g (300 mmol) of metallic sodium was dissolved in 500 ml of methanol with stirring. 17.6 g (100 mmol) of a L-cysteine hydrochloride hydrate was added to the above-prepared reaction solution, followed by stirring at room temperature for one hour. 15.0 g (100 mmol) of 2-fluorobenzyl chloride was added dropwise to the reaction mixture, and then the mixture was further stirred overnight. The solvent was distilled away from the reaction mixture under reduced pressure. The residue thus obtained was dissolved in water and washed with diethyl ether. The resulting water layer was made acid (pH=1) by the addition of concentrated hydrochloric acid, so that crystals separated out.

The crystals were separated from the reaction mixture by filtration, washed with water, ethanol and diethyl ether, and dried over under reduced pressure, whereby 16.5 g of L-S-(2-fluorobenzyl)cysteine was obtained in a yield of 72%.

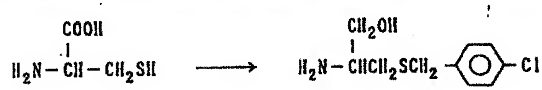
The thus obtained L-S-(2-fluorobenzyl)cysteine was reduced in accordance with the procedure used in

Reference Example 1-46 subsequently, whereby the captioned Reference Compound No. 1-59 was obtained.

NMR (δ, $CDCl_3$): 7.20 - 7.36 (m, 2H), 7.01 - 7.13 (m, 2H), 3.75 (s, 2H), 3.62 (dd, J=11Hz, J=5Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 2.96 - 3.04 (m, 1H), 2.61 (dd, J=13Hz, J=5Hz, 1H), 2.42 (dd, J=13Hz, J=8Hz, 1H), 2.00 - 2.10 (m, 3H)

Reference Example 1-60

Synthesis of (2R)-2-amino-3-(4-chlorobenzylthio)propanol (Reference Compound No. 1-60):

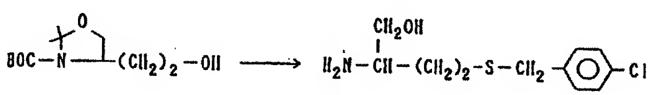


The same reaction procedure as in Reference Example 1-59 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 1-59 was replaced by 4-chlorobenzylchloride, whereby the captioned Reference Compound No. 1-60 was obtained.

NMR (δ, $CDCl_3$): 7.23 - 7.30 (m, 5H), 3.68 (s, 2H), 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 2.92 - 3.00 (m, 1H), 2.54 (dd, J=13Hz, J=5Hz, 1H), 2.36 (dd, J=13Hz, J=8Hz, 1H), 2.16 - 2.28 (m, 3H)

Reference Example 1-61

Synthesis of (2S)-2-amino-4-(4-chlorobenzylthio)butanol (Reference Compound No. 1-61):



2.77 g (27.4 mmol) of triethylamine was added to an ethyl acetate solution containing 5.6 g (22.8 mmol) of the compound synthesized in Reference Example 1-54. 2.2 ml (27.4 mmol) of methanesulfonyl chloride was further added dropwise to the above-prepared reaction mixture under an ice-cooled condition, followed by stirring for two hours. The reaction mixture was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby a methanesulfonate was obtained.

1.05 g (26.2 mmol) of sodium hydride was added to an anhydrous dimethylformamide solution containing 3.72 ml (28.6 mmol) of 4-chlorobenzylmercaptan, followed by stirring at room temperature for 30 minutes. With the addition of 7.7 g (23.8 mmol) of the above prepared methanesulfonate, the reaction mixture was further stirred overnight. With the addition of water, the reaction mixture was extracted with ethyl acetate. A resultant organic extract layer was washed with 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure and the residue thus obtained was chromatographed on a silica gel column for purification, whereby 3.95 g of a 4-chlorobenzylthioether was obtained in a yield of 43%.

8 ml of 4 N HCl - AcOEt was added to a methanol solution containing 3.95 g (10.22 mmol) of the above prepared thioether. This reaction mixture was stirred overnight under an ice-cooled condition. The solvent was distilled away from the reaction mixture under reduced pressure, and the residue thus obtained was dissolved in water and then washed with diethyl ether. A resulting aqueous layer was made bacic by the addition of a 10% potassium carbonate solution, and extracted with chloroform. The extract layer was dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 0.81 g of the captioned Reference Compound No. 1-61 was obtained in a yield of 75%.

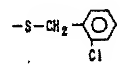
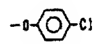
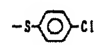
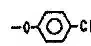
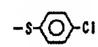
NMR (δ, $CDCl_3$): 7.23 - 7.30 (m, 4H), 3.68 (s, 2H), 3.54 (dd, J=11Hz, J=4Hz, 1H), 3.27 (dd, J=11Hz, J=7Hz, 1H), 2.88 - 2.98 (m, 1H), 2.39 - 2.58 (m, 2H), 1.77 (brs, 3H), 1.64 - 1.74 (m, 1H), 1.45 - 1.55 (m, 1H)

Reference Examples 1-62 to 1-66

The same reaction procedure as in Reference Example 1-61 was repeated except that the 4-chlorobenzylmercaptan used in Reference Example 1-61 was replaced by a mercaptan compound or phenol compound with a moiety R^1 shown in Table 5, and the compound synthesized in Reference Example 1-54 or Reference Example 1-55 was used, whereby Reference Compounds No. 1-62 to No. 1-66 were respectively obtained as shown in Table 5.

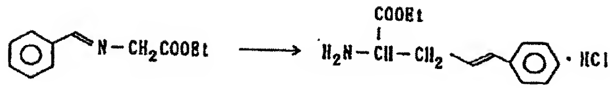
Table 5

$$H_2N\text{-}\underset{}{\overset{CH_2OH}{\overset{|}{CH}}}\text{-}(CH_2)n\text{-}R^1 \qquad \text{(III-b)}$$

Ref. Ex.	Material	Compound	n	R^1	NMR(δ, $CDCl_3$)
1-62	the same as employed in Reference Example 1-54	(2S)-2-amino-4-(2-chloro-benzylthio)butanol	2		7.33 - 7.39 (m, 2H), 7.19 - 7.26 (m, 2H), 3.84 (s, 2H), 3.57 (dd, J=10.69Hz, J=4.01Hz, 1H), 3.29 (dd, J=10.69Hz, J=7.49Hz, 1H), 2.93 - 3.01 (m, 1H), 2.50 - 2.66 (m, 2H), 2.04 (brs, 3H), 1.66 - 1.78 (m, 1H), 1.50 - 1.62 (m, 1H)
1-63	the same as employed in Reference Example 1-54	(2S)-2-amino-4-(4-chloro-phenyloxy)butanol	2		7.22 - 7.31 (m, 2H), 6.81 - 6.98 (m, 2H), 4.04 - 4.12 (m, 2H), 3.61 - 3.67 (m, 1H), 3.36 - 3.43 (m, 1H), 3.10 - 3.18 (m, 1H), 1.88 - 2.00 (m, 3H), 1.68 - 1.82 (m, 2H)
1-64	the same as employed in Reference Exmaple 1-54	(2S)-2-amino-4-(4-chloro-phenylthio)butanol	2		7.32 (d, J=9Hz, 2H), 7.27 (d, J=9Hz, 2H), 4.78 - 4.90 (m, 3H), 3.51 (dd, J=11Hz, J=5Hz, 1H), 3.35 (dd, J=11Hz, J=7Hz, 1H), 2.88 (m, 3H), 1.70 - 1.81 (m, 1H), 1.54 - 1.65 (m, 1H)
1-65	the same as employed in Reference Example 1-55	(2S)-2-amino-5-(4-chloro-phenyloxy)pentanol·hydro-chloric acid	3		(Solvent: CD_3OD) 7.20 - 7.30 (m, 2H), 6.85 - 6.95 (m, 2H), 4.01 (t, J=6Hz, 2H), 3.80 (dd, J=11Hz, 3Hz, 1H), 3.60 (dd, J=11Hz, 6Hz, 1H), 3.25 - 3.35 (m, 1H), 1.75 - 2.00 (m, 4H)
1-66	the same as employed in Refernece Example 1-55	(2S)-2-amino-5-(4-chloro-phenylthio)pentanol	3		7.22 - 7.35 (m, 5H), 3.49 (dd, J=10Hz, 4.5Hz, 1H), 2.94 (t, J=7Hz, 2H), 2.65 - 2.80 (m, 1H), 1.50 - 1.85 (m, 3H), 1.30 - 1.50 (m, 1H)

Reference Example 1-67

Synthesis of (2R,2S)-2-amino-5-phenyl-4-pentenoic acid ethyl ester hydrochloride (Reference Compound No. 1-67):



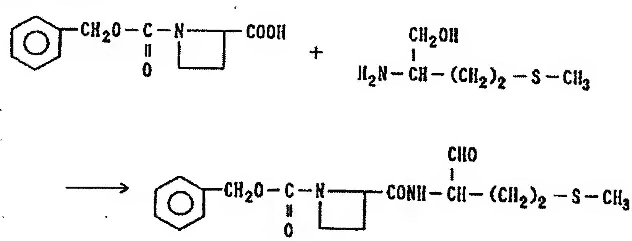
9.32 ml (15.0 mmol) of a hexane solution containing n-butyl lithium was added dropwise to an anhydrous tetrahydrofuran solution of 2.31 ml (16.5 mmol) of diisopropylamine at -78°C in a stream of nitrogen. After the completion of dropping, the reaction mixture was stirred at room temperature for one hour. To this reaction mixture, an anhydrous tetrahydrofuran solution containing 2.868 g (15.0 mmol) of benzylideneglycine ethyl ester was added at -78°C. After stirring for one hour, 1.82 ml (15.0 mmol) of cinnamyl bromide was added to the reaction mixture. The reaction mixture was stirred at -78°C for 4 hours and then at room temperature overnight.

After putting into 150 ml of a cooled saturated ammonium chloride solution, the reaction mixture was extracted with ether and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure. To the residue thus obtained, 40 ml of 5% hydrochloric acid was added, followed by stirring for two hours. Furthermore, with the addition of 40 ml of 5% hydrochloric acid, the residue was washed with ether. The resulting water layer was made basic with a sodium hydrogencarbonate solution thereto and extracted with ethyl acetate. The extract layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. With the addition of 5.5 ml of a mixture of 4 N HCl - AcOEt thereto, the solvent was distilled away under reduced pressure, whereby 2.54 g of the captioned Reference Compound No. 1-67 was obtained in a yield of 66%.

NMR (δ, $CDCl_3$): 8.50 - 8.90 (m, 2H), 7.11 - 7.50 (m, 5H), 6.54 (d, J=15.6Hz, 6.22 (dt, J=15.8Hz, J=8.2Hz, 1H), 4.00 - 4.25 (m, 3H), 2.80 - 3.10 (m, 2H), 1.18 (t, J=7.1Hz, 3H)

Example 1-1

Synthesis of (2R,2S)-1-benzyloxycarbonyl-azetidine-2-carboxylic acid-(1S)-(1-formyl-3-methylthio)-propylamide (Compound No. 1-1):



100 ml of a methylene chloride solution containing 1.27 g (5.4 mmol) of Reference Compound No. 1-1 synthesized in Reference Example 1-1, 0.826 g (5.4 mmol) of a N-hydroxybenzotriazole hydrate, 0.546 g (5.4 mmol) of triethylamine and 0.73 g (5.4 mmol) of Reference Compound No. 1-46 synthesized in Reference Example 1-46 was cooled in an ice bath containing sodium chloride. 20 ml of a methylene chloride solution containing 1.22 (5.94 mmol) of N,N'-dicyclohexylcarbodiimide was added dropwise to the above-prepared reaction mixture, followed by stirring for 18 hours.

Insoluble materials were removed from the reaction mixture by filtration. The filtrate was washed successively with 1 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate, and a saturated aqueous solution of sodium chloride. An organic layer and a water layer in the thus washed filtrate were separated. The resulting water layer was extracted with methylene chloride again to obtain an another organic layer. The thus extracted organic layer and the first obtained organic layer were mixed, dried over

anhydrous sodium sulfate. and concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 1.28 g of (2R,S)-1-benzyloxycarbonyl-azetidine-2-carboxylic acid-(1S)-(hydroxymethyl-3-methylthio)-propylamide was obtained in a yield of 67%.

10 ml of an anhydrous dimethyl sulfoxide of 1.42 g (8.95 mmol) of pyridine•sulfur trioxide complex was added dropwise to 20 ml of an anhydrous dimethyl sulfoxide solution containing the above prepared (2R,S)-1-benzyloxycarbonyl-azetidine-2-carboxylic acid-(1S)-(hydroxymethyl-3-methylthio)propylamide and 0.905 (8.75 mmol) of triethylamine. The reaction mixture was then stirred for 30 minutes and added to an iced water. The reaction mixture was extracted with ethyl acetate four times. The resultant extract organic layer was washed successively with a 10% citric acid solution, water, a saturated aqueous solution of sodium hydrogencarbonate, and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 1.03 g of the captioned Compound No. 1-1 in the state of a mixture of diastereomers was obtained as an oily material in a yield of 80%.

NMR (δ, $CDCl_3$): 9.59 - 9.62 (m, 1H), 7.50 - 8.10 (bs, 1H), 7.30 - 7.45 (m, 5H), 5.05 - 5.20 (m, 2H), 4.70 - 4.85 (m, 1H), 4.45 - 4.65 (m, 1H), 3.85 - 4.10 (m, 2H), 2.35 - 2.70 (m, 4H), 1.90 - 2.30 (m, 5H)

R_f values: 0.34 (Developing Solvent A: ethyl acetate)
0.16 (Developing Solvent B: mixture of methylene chloride and acetone at a mixing ratio of 10:1)

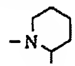
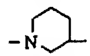
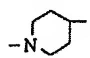
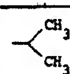
Examples 1-2 to 1-21

The same reaction procedure as in Example 1-1 was repeated except that the carboxylic acid derivative (Reference Compound No. 1-1 synthesized in Reference Example 1-1) and the amine derivative (Reference Compound No. 1-46 synthesized in Reference Example 1-46) used in Example 1-1 were respectively replaced by a carboxylic acid derivative (Material 1) and an amine derivative (Material 2) shown in Table 6, whereby Compounds No. 1-2 to No. 1-21 (cyclic carboxylic acid amide derivatives) shown in Table 6 were obtained.

Furthermore, Table 7 shows the yield, the melting point or state, the NMR analysis data and the R_f values obtained by TLC analysis of each of the thus prepared cyclic carboxylic acid amide derivatives. The developing solvent A used in the TLC analysis is ethyl acetate and the developing solvent B is a mixture of methylene chloride and acetone at a mixing ratio of 10:1.

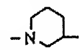
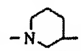
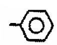
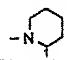
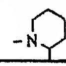
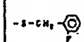
Table 6

 $-CH_2OC(=O)-Y-CONH-CH(CHO)-(CH_2)n-R^1$ (I-a)

Ex.	Material 1 (*)	Material 2 (*)	Y	n	R^1	Compound
1-2	cbz-L-proline	1-46		2	$-S-CH_3$	(2S)-1-benzyloxycarbonylpyrrolidine-2-carboxylic acid-(1S)-(1-formyl-3-methylthio)propylamide
1-3	1-2	1-46		2	$-S-CH_3$	(2R, 2S)-1-benzyloxycarbonylpiperidine-2-carboxylic acid-(1S)-(1-formyl-3-methylthio)propylamide
1-4-a	1-3	1-46		2	$-S-CH_3$	1-benzyloxycarbonylpiperidine-3-carboxylic acid-(1S)-(1-formyl-3-methylthio)propylamide
1-4-b	1-3	1-46		2	$-S-CH_3$	the same as the diastereomer compound employed in Example 1-4-a
1-5	1-4	1-46		2	$-S-CH_3$	1-benzyloxycarbonylpiperidine-4-carboxylic acid-(1S)-(1-formyl-3-methylthio)propylamide
1-6	1-4	1-47		1		1-benzyloxycarbonylpiperidine-4-carboxylic acid-(1S)-(3-methyl)butylamide

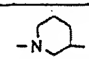
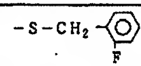
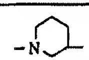
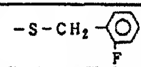
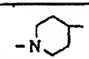
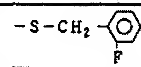
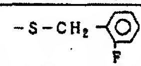
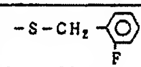
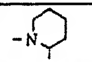
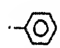
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 6

Ex.	Material 1 (*)	Material 2 (*)	Y	n	R^1	Compound
1-7	1-4	1-48		1		1-benzyloxycarbonylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-8-a	1-3	1-48		1		1-benzyloxycarbonylpiperidine-3-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-8-b	1-3	1-48		1		the same as the diastereomer compound employed in Example 1-8-a
1-9	1-2	1-48		1		(2R, 2S)-1-benzyloxycarbonylpiperidine-2-carboxylic acid-(1-formyl-2-phenyl)ethylamide
1-10	cbz-L-proline	1-48		1		(2S)-1-benzyloxypyrrolidine-2-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-11	1-1	1-48		1		(2R, 2S)-1-benzyloxycarbonylazetidine-2-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-12	1-2,	1-59		1		(2R, 2S)-1-benzyloxycarbonylpiperidine-2-carboxylic acid-(1R)-[1-formyl-2-(2-fluorobenzyl)thio]ethylamide

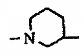
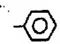
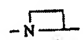
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 6

Ex.	Material 1 (*)	Material 2 (*)	Y	n	R[1]	Compound
1-13 -a	1-3	1-59		1		1-benzyloxycarbonylpiperidine-3-carboxylic acid (1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
1-13 -b	1-3	1-59		1		the same as the diastereomer compound employed in Example 1-13-a
1-14	1-4	1-59		1		1-benzyloxycarbonylpiperidine-4-carboxylic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
1-15	cbz-L-proline	1-59		1		(2S)-1-benzyloxycarbonylpyrrolidine-2-carboxylic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
1-16	1-1	1-59		1		(2R, 2S)-1-benzyloxycarbonylazetidine-2-carboxylic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]-ethylamide
1-17	1-2	1-50		2		(2R; 2S)-1-benzyloxycarbonylpiperidine-2-carboxylic acid-(1S)-(1-formyl-3-phenyl)propylamide

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 6

Ex.	Material 1 (*)	Material 2 (*)	Y	n	R^1	Compound
1-18 -a	1-3	1-50		2		1-benzyloxycarbonylpiperidine-3-carboxylic acid-(1S)-(1-formyl-3-phenyl)propylamide
1-18 -b	1-3	1-50		2		the same as the diastereomer compound employed in Example 1-18-a
1-19	1-4	1-50		2		1-benzyloxycarbonylpiperidine-4-carboxylic acid-(1S)-(1-formyl-3-phenyl)propylamide
1-20	cbz-L-proline	1-50		2		(2S)-1-benzyloxycarbonylpyrrolidine-2-carboxylic acid-(1S)-(1-formyl-3-phenyl)propylamide
1-21	1-1	1-50		2		(2R, 2S)-1-benzyloxycarbonylazetidine-2-carboxylic acid-(1S)-(1-formyl-3-phenyl)propylamide

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 7

Ex.	Yield (%)	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-2	80	oily	9.60 - 9.80 (m, 1H), 7.30 - 7.50 (m, 5H) 5.17 (s, 2H), 4.30 - 4.60 (m, 2H), 3.35 - 3.70 (m, 2H), 1.80 - 2.60 (m, 8H), 2.03 (s, 3H)	A: 0.37 B: 0.16
1-3	65	oily	9.58 - 9.60 (m, 1H), 7.30 - 7.45 (m, 5H) 6.60 - 6.90 (m, 1H), 5.10 - 5.30 (m, 2H) 4.80 - 4.75 (m, 1H), 4.50 - 4.70 (m, 1H) 4.05 - 4.30 (m, 1H), 2.80 - 3.10 (m, 1H) 2.40 - 2.60 (m, 2H), 2.15 - 2.35 (m, 2H) 2.04 (s, 3H), 1.35 - 1.80 (m, 6H)	A: 0.52 B: 0.17
1-4 -a	25	oily	9.50 - 9.61 (m, 1H), 7.30 - 7.40 (m, 5H) 6.20 - 7.00 (m, 1H), 5.05 - 5.20 (m, 2H) 4.50 - 4.60 (m, 1H), 2.70 - 4.30 (m, 4H) 2.15 - 2.60 (m, 4H), 2.08 (s, 3H), 1.40 - 2.05 (m, 5H)	A: 0.41 B: 0.20
1-4 -b	33	oily	9.50 - 9.65 (m, 1H), 7.25 - 7.50 (m, 5H) 6.10 - 6.90 (m, 1H), 5.10 - 5.20 (m, 2H) 4.50 - 4.60 (m, 1H), 2.80 - 4.25 (m, 4H) 1.40 - 2.65 (m, 9H), 2.07 (s, 3H)	A: 0.41 B: 0.17
1-5	46	amorphous	9.63 (s, 1H), 7.30 - 7.40 (m, 5H), 6.34 (d, J=6Hz, 1H), 5.12 (s, 2H), 4.61 (q, J=7Hz, 1H), 4.10 - 4.35 (m, 2H), 2.75 - 3.95 (m, 2H), 2.15 - 2.65 (m, 4H), 2.08 (s, 3H), 1.55 - 2.10 (5H)	A: 0.33 B: 0.12
1-6	50	amorphous	9.58 (s, 1H), 7.25 - 7.44 (m, 5H), 5.89 - 6.03 (m, 1H), 5.13 (s, 2H), 4.56 - 4.67 (m, 1H), 4.10 - 4.32 (m, 2H), 2.72 - 2.97 (m, 2H), 2.35 (tt, J=11.3Hz, J=3.8Hz, 1H), 1.35 - 1.95 (m, 7H), 0.97 (d, J=6.2Hz, 3H), 0.96 (d, J=6.4Hz, 3H)	A: 0.40 B: 0.18
1-7	46	118.1 to 124.5°C	9.65 (m, 1H), 7.01 - 7.46 (m, 10H), 5.92 - 6.06 (m, 1H), 5.12 (s, 2H), 4.71 - 4.81 (m, 1H), 4.04 - 4.30 (m, 2H), 3.19 (d, J=6.5Hz, 2H), 2.70 - 2.93 (m, 2H), 2.28 (tt, J=11.4Hz, J=3.9Hz, 1H), 1.45 - 1.89 (m, 4H)	A: 0.37 B: 0.13

Table 7

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-8-a	32	124.9 to 130.3°C	9.59 (s, 1H), 7.24 - 7.36 (m, 8H), 7.14 (m, 2H), 6.50 (brs, 1H), 5.12 (s, 2H), 4.69 (q, J=6Hz, 1H), 3.70 - 4.20 (m, 2H) 3.06 - 3.20 (m, 4H), 2.23 - 2.38 (m, 1H), 1.72 - 1.90 (m, 1H), 1.67 (m, 2H), 1.34 - 1.65 (m, 1H)	A: 0.43 B: 0.13
1-8-a	38	oily	9.61 (s, 1H), 7.20 - 7.40 (m, 8H), 7.13 (m, 2H), 6.40 (brs, 1H), 5.11 (s, 2H), 4.65 - 4.75 (m, 1H), 3.80 - 4.10 (m, 2H) 3.06 - 3.20 (m, 4H), 2.22 - 2.39 (m, 1H) 1.70 - 1.95 (m, 1H), 1.62 (m, 2H), 1.37 - 1.55 (m, 1H)	A: 0.42 B: 0.15
1-9	50	oily	9.61 (s, 1H), 7.20 - 7.40 (m, 8H), 7.10 (d, J=7Hz, 2H), 6.55 (brs, 1H), 5.14 (s, 2H), 4.82 (m, 1H), 4.64 - 4.72 (m, 1H), 3.75 - 4.20 (m, 1H), 2.93 - 3.25 (m, 1H), 2.75 - 2.93 (m, 1H), 2.20 - 2.50 (m, 1H), 1.23 - 1.75 (m, 6H)	A: 0.54 B: 0.23
1-10	78	70.8 to 74.7°C	9.61 (s, 1H), 7.10 - 7.45 (m, 8H), 7.09 (brs, 2H), 6.39 (brs, 1H), 5.11 (q, J= 12Hz, 1H), 4.64 (m, 1H), 4.36 (m, 1H), 3.27 - 3.55 (m, 2H), 2.90 - 3.25 (m, 2H) 1.50 - 2.40 (m, 4H)	A: 0.41 B: 0.14
1-11	51	oily	9.61 (s, 1H), 7.10 - 7.40 (m, 10H), 5.09 (s, 2H), 4.65 - 4.74 (m, 2H), 3.87 - 4.10 (m, 1H), 3.79 (q, J=8Hz, 1H), 3.18 (dd, J=14Hz, J=6Hz, 1H), 3.02 (dd, J= 14Hz, J=7Hz, 1H), 2.45 (m, 2H), 1.70 (m, 1H)	A: 0.36 B: 0.14
1-12	66	oily	9.50 - 9.55 (m, 1H), 7.20 - 7.45 (m, 7H) 7.00 - 7.15 (m, 2H), 6.50 - 7.00 (bs, 1H), 5.18 (s, 2H), 4.80 - 5.00 (m, 1H), 4.50 - 4.65 (m, 1H), 4.00 - 4.30 (m, 1H) 3.65 - 3.80 (m, 2H), 2.70 - 3.10 (m, 3H) 2.25 - 2.35 (m, 1H), 1.30 - 1.90 (m, 5H)	A: 0.56 B: 0.36

Table 7

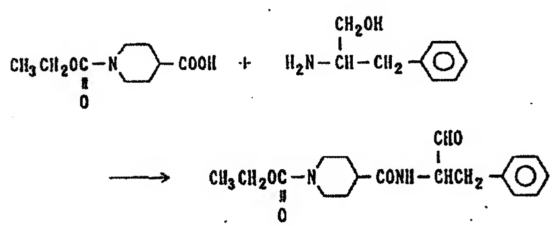
Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-13-a	27	amorphous	9.45 - 9.60 (m, 1H), 7.20 - 7.45 (m, 7H) 7.00 - 7.15 (m, 2H), 6.10 - 6.90 (m, 1H) 5.05 - 5.20 (m, 2H), 4.45 - 4.60 (m, 1H) 3.80 - 4.25 (m, 2H), 3.75 (s, 2H), 3.00 - 3.40 (m, 2H), 2.70 - 3.00 (m, 2H), 2.20 - 2.50 (m, 1H), 1.40 - 2.00 (m, 4H)	A: 0.46 B: 0.17
1-13-b	30	oily	9.45 - 9.60 (m, 1H), 7.20 - 7.45 (m, 7H) 7.00 - 7.15 (m, 2H), 6.20 - 7.00 (m, 1H) 5.00 - 5.20 (m, 2H), 4.45 - 4.60 (m, 1H) 3.80 - 4.20 (m, 2H), 3.74 (d, J=3Hz, 2H) 2.90 - 3.40 (m, 2H), 2.70 - 3.00 (m, 2H) 2.25 - 3.45 (m, 1H), 1.40 - 2.00 (m, 4H)	A: 0.45 B: 0.17
1-14	46	amorphous	9.50 (s, 1H), 7.20 - 7.45 (m, 7H), 7.00 - 7.15 (m, 2H), 6.25 - 6.45 (m, 1H), 5.13 (s, 2H), 4.63 (q, J=6Hz, 1H), 4.10 - 4.30 (m, 2H), 3.76 (s, 2H), 2.75 - 3.05 (m, 4H), 2.34 (tt, J=10Hz, 4Hz, 1H) 1.50 - 1.90 (m, 4H)	A: 0.39 B: 0.11
1-15	44	oily	9.30 - 9.60 (m, 1H), 7.20 - 7.55 (m, 8H) 7.00 - 7.17 (m, 2H), 5.05 - 5.57 (m, 2H) 4.30 - 4.60 (m, 2H), 3.35 - 3.85 (m, 4H) 2.70 - 3.00 (m, 2H), 1.85 - 2.30 (m, 4H)	A: 0.42 B: 0.21
1-16	18	oily	9.50 - 9.65 (m, 1H), 7.20 - 7.40 (m, 8H) 7.00 - 7.20 (m, 2H), 5.05 - 5.25 (m, 2H) 4.70 - 4.85 (m, 1H), 4.50 - 4.60 (m, 1H) 3.65 - 4.10 (m, 4H), 2.80 - 3.00 (m, 2H) 2.50 - 2.70 (m, 2H)	A: 0.33 B: 0.14
1-17	59	oily	9.50 (s, 1H), 7.05 - 7.45 (m, 10H), 6.30 - 6.80 (m, 1H), 5.21 (m, 2H), 4.88 (m, 2H), 4.35 - 4.60 (m, 1H), 4.00 - 4.30 (m, 1H), 2.80 - 3.08 (m, 1H), 2.63 (t, J=7.8Hz, 2H), 2.10 - 2.38 (m, 2H), 1.30 - 2.00 (m, 6H)	A: 0.54 B: 0.40
1-18-a	14	amorphous	9.47 (s, 1H), 7.00 - 7.45 (m, 10H), 5.90 - 6.80 (m, 1H), 5.13 (s, 2H), 4.36 - 4.60 (m, 1H), 1.00 - 4.30 (m, 13H)	A: 0.53 B: 0.23

Table 7

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-18-b	13	amorphous	9.50 (s, 1H), 7.12 - 7.44 (m, 10H), 5.80 - 6.70 (m, 1H), 5.06 - 5.21 (m, 2H), 4.43 - 4.59 (m, 1H), 2.75 - 4.24 (m, 4H) 2.66 (t, J=7.7Hz, 2H), 1.40 - 2.55 (m, 7H)	A: 0.48 B: 0.24
1-19	5.8	amorphous	9.53 (s, 1H), 7.12 - 7.41 (m, 10H), 6.00 - 6.13 (m, 1H), 5.13 (s, 2H), 4.54 - 4.64 (m, 1H), 4.07 - 4.33 (m, 2H), 2.50 - 2.95 (m, 4H), 2.21 - 2.39 (m, 2H), 1.52 - 2.08 (m, 5H)	A: 0.41 B: 0.14
1-20	89	amorphous	9.20 - 9.60 (m, 1H), 7.00 - 7.50 (m, 10H), 6.35 - 6.55 (m, 1H), 5.18 (s, 2H), 4.25 - 4.55 (m, 2H), 3.35 - 3.70 (m, 2H) 1.50 - 2.85 (m, 8H)	A: 0.42 B: 0.26
1-21	49	oily	9.52 (s, 0.5H), 9.50 (s, 0.5H), 7.00 - 7.60 (m, 11H), 5.05 - 5.25 (m, 2H), 4.65 - 4.88 (m, 1H), 4.30 - 4.60 (m, 1H), 3.80 - 4.12 (m, 2H), 2.66 (t, J=7.8Hz, 2H), 1.40 - 2.85 (m, 4H)	A: 0.36 B: 0.25

Example 1-22

Synthesis of 1-ethoxycarbonylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide (Compound No. 1-22):



50 ml of a chloroform solution containing 0.84 g (4.17 mmol) of 1-ethoxycarbonylpiperidine-4-carboxylic acid synthesized in Reference Example 1-5 was cooled in an ice bath containing sodium chloride. 0.61 ml (4.38 mmol) of triethylamine and 0.38 ml (3.97 mmol) of ethyl chlorocarbonate were successively added to the above solution. After stirring for 30 minutes, a chloroform solution containing 0.6 g (3.97 mmol) of (2S)-2-amino-3-phenylpropanol synthesized in Reference Example 1-48 was added to the above prepared reaction mixture. The reaction mixture was stirred for one hour at -10°C and further stirred overnight at

room temperature.

The reaction mixture was washed successively with a 1 N hydrochloric acid solution, a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium hydrogencarbonate and then a saturated aqueous solution of sodium chloride. The solvent was distilled away under reduced pressure. The residue thus obtained was crystallized in isopropyl ether and then the crystals were separated by filtration.

0.95 g (2.84 mmol) of the thus obtained crystals was dissolved in 10 ml of dimethyl sulfoxide, 1.60 ml (11.4 mmol) of triethylamine was added thereto. Furthermore, 10 ml of a dimethyl sulfoxide solution in which 1.81 g (11.4 mmol) of pyridine sulfur trioxide was added dropwise to the above reaction mixture. After stirring for one hour, the reaction mixture was poured into 10 ml of iced water and extracted with ethyl acetate. The extract layer was washed successively with a 10% cirtic acid solution, a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride. The resultant organic extract layer was dried over anhydrous sodium sulfate and the solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.53 g of the captioned Compound No. 1-22 was obtained as crystals in a yield of 41%.

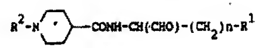
Melting Point (°C):	74.1 to 77.8
NMR (δ, $CDCl_3$):	9.65 (s, 1H), 7.09 - 7.37 (m, 5H), 5.95 - 6.14 (m, 1H), 4.70 - 4.82 (m, 1H), 4.13 (q, J=7.1Hz, 2H), 4.00 - 4.26 (m, 2H), 3.19 (d, J=6.4Hz, 2H), 2.65 - 2.90 (m, 2H), 2.28 (tt, J=11.4Hz, J=3.9Hz, 1H), 1.43 - 1.86 (m, 4H), 1.26 (t, J=7.1Hz, 3H)
R_f values:	0.13 (B) 0.31 (A)

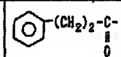
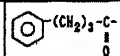
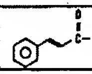
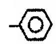
Examples 1-23 to 1-90

The same reaction procedure as in Example 1-22 was repeated except that the carboxylic acid derivative (the compound synthesized in Reference Example 1-5) and the amine derivative (the compound synthesized in Reference Example 1-48) used in Example 1-22 were respectively replaced by a carboxylic acid derivative (Material 1) and an amine derivative (Material 2) shown in Table 8, whereby Compound No. 1-23 to No. 1-90 (cyclic carboxylic acid amide derivative) shown in Table 8 were obtained.

Table 9 shows the yield, the melting point or state, the NMR analysis data and the R_f values obtained by TLC analysis of each cyclic carboxylic acid amide derivative. The developing solvent A used in the TLC analysis is ethyl acetate and the developing solvent B is a mixture of methylene chloride and acetone at a mixing ratio of 10:1.

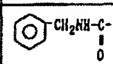
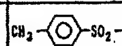
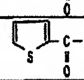
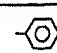
Table 8



Ex.	Material 1 (*)	Materiel 2 (*)	R^2	n	R^1	Compound
1-23	1-6	1-48		1		1-benzoylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-24	1-7	1-48		1		1-phenylacetylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-25	1-8	1-48		1		1-(3-phenylpropionyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-26	1-9	1-48		1		1-(4-phenylbutyryl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-27	1-10	1-48		1		1-cinnamoylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide

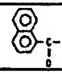
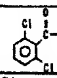
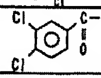
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-28	1-12	1-48		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-29	1-27	1-48		1		1-(N-benzylcarbamoyl)piperidine-4-carboxylic acid (1S)-(1-formyl-2-phenyl)ethylamide
1-30	1-29	1-48		1		1-(4-methylphenylsulfonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-31	1-13	1-48		1		1-cyclopentylcarbonylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-32	1-14	1-48		1		1-(2-thienylcarbonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide

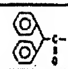
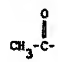
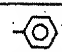
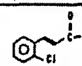
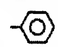
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-33	1-11	1-48		1		1-(1-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-34	1-30	1-48		1		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-35	1-32	1-48		1		1-(2,6-dichlorobenzoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-36	1-17	1-48		1		1-(3,4-dichlorobenzoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-37	1-15	1-48	$(CH_3)_3C-C(=O)-$	1		1-trimethylacetylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide

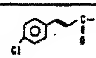
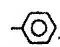
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-38	1-31	1-48		1		1-(diphenylacetyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-39	1-33	1-48		1		1-(9-fluorenylcarbonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-40	1-16	1-48		1		1-acetylpiperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-41	1-28	1-48		1		1-(N-phenylcarbamoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-42	1-18	1-48		1		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide

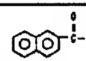
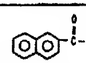
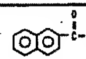
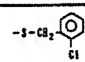
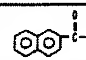
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-43	1-19	1-48		1		1-(3-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-44	1-20	1-48		1		1-(4-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-45	1-12	1-51		3	$-CH_3$	1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-1-formyl-pentylamide
1-46	1-12	1-56		3		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-4-phenyl)butylamide
1-47	1-12	1-57		4		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-5-phenyl)pentylamide

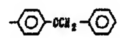
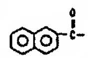
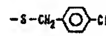
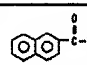
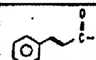
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-48	1-12	1-58		5		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-6-phenyl)hexylamide
1-49	1-12	1-52		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-50	1-12	(S)-2-phenyl-glycinol		0		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-1-phenyl)methylamide
1-51	1-12	1-62		2		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(2-chlorobenzylthio)]propylamide
1-52	1-12	1-46		2	$-S-CH_3$	1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-3-methylthio)propylamide

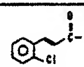
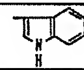
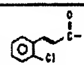
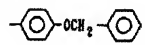
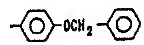
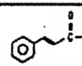
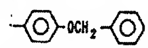
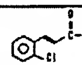
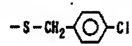
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-53	1-12	1-49		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethylamide
1-54	1-12	1-60		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1R)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide
1-55	1-12	1-53		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(2-fluorophenyl)]ethylamide
1-56	1-30	1-52		1		1-(2-naphtylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-57	1-10	1-52		1		1-cinnamoylpiperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide

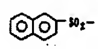
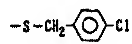
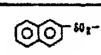
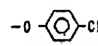
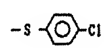
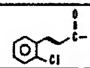
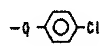
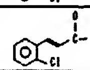
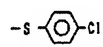
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-58	1-18	1-52		1		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-59	1-18	1-49		1		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethyl-amide
1-60	1-30	1-49		1		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethyl-amide
1-61	1-10	1-49		1		1-cinnamoylpiperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethyl
1-62	1-18	1-61		2		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorobenzylthio)]-propylamide

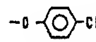
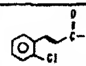
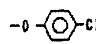
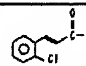
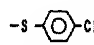
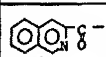
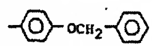
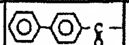
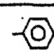
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-63	1-30	1-61		2		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorobenzylthio)]-propylamide
1-64	1-30	1-65		3		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-4-(4-chlorophenyloxy)]butyl-amide
1-65	1-30	1-66		3		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-4-(4-chlorophenylthio)]butyl-amide
1-66	1-18	1-65		3		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-4-(4-chlorophenyloxy)]butyl-amide
1-67	1-18	1-66		3		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-4-(4-chlorophenylthio)]butyl-amide

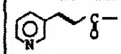
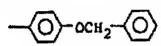
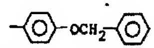
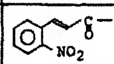
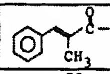
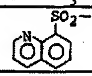
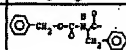
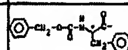
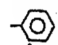
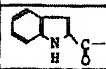
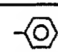
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-68	1-30	1-63		2		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorophenyloxy)]propylamide
1-69	1-30	1-64		2		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorophenylthio)] propylamide
1-70	1-18	1-63		2		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorophenyloxy)]propylamide
1-71	1-18	1-64		2		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-3-(4-chlorophenylthio)]-propylamide
1-72	1-34	1-48		1		1-(2-quinolylcarbonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-73	1-35	1-52		1		1-(3-quinolylcarbonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-74	1-36	1-49		1		1-(3-isoquinolylcarbonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethylamide
1-75	1-21	1-48		1		1-(4-phenylbenzoyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide

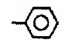
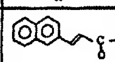
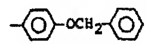
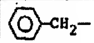
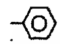
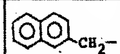
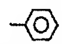
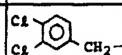
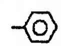
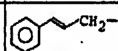
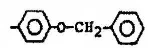
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R^2	n	R^1	Compound
1-76	1-37	1-49		1		1-[3-(3-pyridyl)acryloyl]piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethylamide
1-77	1-22	1-49		1		1-[3-(3-thienyl)acryloyl]piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxyphenyl)]ethylamide
1-78	1-23	1-52		1		1-(2-nitrocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-79	1-24	1-52		1		1-[(3-phenyl-2-methyl)acryloyl]piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]-ethylamide
1-80	1-25	1-48		1		1-(8-quinolylsulfonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-81	1-40	1-48		1		1-(benzyloxycarbonyl-L-phenylalanyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-82	1-41	1-48		1		1-(benzyloxycarbonyl-D-phenylalanyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-83	1-38	1-48		1		1-(2-indolylcarbonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamid

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 8

Ex.	Material 1 (*)	Material 2 (*)	R²	n	R¹	Compound
1-84	1-39	1-48		1		1-(3-indolylcarbonyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-85	1-26	1-49		1		1-(2-naphthylacryloyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxy)phenyl]ethylamide
1-86	1-43	1-48		1		1-benzyl-piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-87	1-42	1-48		1		1-(2-naphthylmethyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-88	1-42	1-52		1		1-(2-naphthylmethyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide
1-89	1-44	1-48		1		1-(3,4-dichlorobenzyl)piperidine-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide
1-90	1-45	1-49		1		1-cinnamyl-piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-benzyloxy)phenyl]ethylamide

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-23	40	amorphous	9.65 (s, 1H), 7.09 - 7.49 (m, 10H), 6.02 - 6.21 (m, 1H), 4.35 - 4.90 (m, 2H), 3.60 - 3.95 (m, 1H), 3.19 (d, J=6.3Hz, 2H), 2.60 - 3.20 (m, 2H), 2.28 - 2.46 (m, 1H), 1.40 - 2.00 (m, 4H)	A: 0.16 B: 0.05
1-24	51	109.9 to 114.1°C	9.64 (s, 1H), 7.05 - 7.45 (m, 10H), 5.93 - 6.09 (m, 1H), 4.67 - 4.80 (m, 1H), 4.50 - 4.67 (m, 1H), 3.78 - 3.95 (m, 1H) 3.73 (s, 2H), 3.17 (d, J=6.5Hz, 2H), 2.90 - 3.07 (m, 1H), 2.60 - 2.76 (m, 1H) 2.29 (tt, J=11.5Hz, J=4.0Hz, 1H), 1.30 - 1.90 (m, 4H)	A: 0.14 B: 0.05
1-25	38	110.8 to 112.7°C	9.64 (s, 1H), 7.08 - 7.40 (m, 10H), 5.90 - 6.10 (m, 1H), 4.69 - 4.82 (m, 1H), 4.35 - 4.75 (m, 1H), 3.60 - 3.95 (m, 1H) 3.19 (d, J=6.5Hz, 2H), 2.96 (t, J=8.0Hz, 2H), 2.62 (t, J=7.8Hz, 2H), 2.45 - 3.10 (m, 2H), 2.31 (tt, J=11.3Hz, J=3.8Hz, 1H), 1.35 - 1.90 (m, 4H)	A: 0.16 B: 0.06
1-26	38	amorphous	9.62 (s, 1H), 7.07 - 7.38 (m, 10H), 5.95 - 6.18 (m, 1H), 4.68 - 4.81 (m, 1H), 4.20 - 4.80 (m, 1H), 3.50 - 4.10 (m, 1H) 3.19 (d, J=6.5Hz, 2H), 2.68 (t, J=7.4Hz, 2H), 2.45 - 3.15 (m, 2H), 2.32 (t, J=7.6Hz, 2H), 2.25 - 2.41 (m, 1H), 1.97 (t, J=7.5Hz, 2H), 1.40 - 1.90 (m, 4H)	A: 0.16 B: 0.06
1-27	70	amorphous	9.66 (s, 1H), 7.65 (d, J=15.5Hz, 1H), 7.09 - 7.60 (m, 10H), 6.87 (d, J=15.5Hz, 1H), 6.00 - 6.15 (m, 1H), 4.70 - 4.85 (m, 1H), 3.95 - 4.85 (m, 2H), 3.20 (d, J=6.4Hz, 2H), 2.60 - 3.35 (m, 2H), 2.40 (tt, J=11.2Hz, J=4.0Hz, 1H), 1.58 - 2.05 (m, 4H)	A: 0.16 B: 0.05
1-28	59	amorphous	9.65 (s, 1H), 7.80 - 7.95 (m, 4H), 7.42 - 7.65 (m, 3H), 7.09 - 7.40 (m, 5H), 6.00 - 6.20 (m, 1H), 4.70 - 4.84 (m, 1H) 3.60 - 4.90 (m, 2H), 3.20 (d, J=6.5Hz, 2H), 2.70 - 3.15 (m, 2H), 2.34 - 2.48 (m, 1H), 1.40 - 4.90 (m, 4H)	A: 0.17 B: 0.05

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-29	56	163.8 to 185.1°C	9.65 (s, 1H), 7.08 - 7.42 (m, 10H), 5.95 - 6.10 (m, 1H), 4.65 - 4.83 (m, 2H), 4.42 (s, 2H), 3.87 - 4.03 (m, 2H), 3.19 (d, J=6.5Hz, 2H), 2.75 - 2.93 (m, 2H), 2.29 (tt, J=11.3Hz, J=4.0Hz, 1H), 1.50 - 1.87 (m, 4H)	A: 0.36 B: 0.11
1-30	44	101.9 to 116.6°C	9.61 (s, 1H), 7.56 - 7.70 (m, 2H), 7.05 - 7.45 (m, 7H), 5.90 - 6.08 (m, 1H), 4.67 - 4.80 (m, 1H), 3.65 - 3.81 (m, 2H) 3.16 (d, J=6.5Hz, 2H), 2.43 (s, 3H), 2.28 - 2.42 (m, 2H), 2.00 - 2.13 (m, 1H) 1.60 - 1.90 (m, 4H)	A: 0.45 B: 0.22
1-31	46	oil	9.63 (s, 1H), 7.08 - 7.43 (m, 5H), 6.03 - 6.30 (m, 1H), 4.65 - 4.84 (m, 1H), 3.75 - 4.85 (m, 2H), 3.19 (d, J=6.3Hz, 2H), 2.45 - 3.29 (m, 3H), 2.28 - 2.45 (m, 1H), 1.47 - 2.05 (m, 12H)	A: 0.22 B: 0.09
1-32	47	amorphous	9.63 (s, 1H), 7.44 (dd, J=5.1Hz, J=1.1Hz, 1H), 7.20 - 7.38 (m, 4H), 7.13 (d, J=7.1Hz, 2H), 7.04 (dd, J=5.0Hz, J=3.6Hz, 1H), 6.10 - 6.32 (m, 1H), 4.76 (q, J=6.6Hz, 1H), 4.20 - 4.58 (m, 2H), 3.20 (d, J=6.6Hz, 2H), 2.86 - 3.17 (m, 2H), 2.42 (tt, J=11.0Hz, J=4.2Hz, 1H), 1.55 - 2.00 (m, 4H)	A: 0.23 B: 0.12
1-33	56	amorphous	9.62 (s, 1H), 7.00 - 7.95 (m, 12H), 6.09 - 6.28 (m, 1H), 4.68 - 4.93 (m, 2H), 3.30 - 3.55 (m, 1H), 3.10 - 3.27 (m, 2H) 2.70 - 3.09 (m, 2H), 2.29 - 2.46 (m, 1H) 1.40 - 2.05 (m, 4H)	A: 0.21 B: 0.07
1-34	44	137.6 to 143.9°C	9.59 (s, 1H), 8.33 (s, 1H), 7.89 - 8.04 (m, 3H), 7.58 - 7.78 (m, 3H), 7.03 - 7.35 (m, 5H), 5.90 - 6.10 (m, 1H), 4.71 (q, J=6.6Hz, 1H), 3.77 - 3.92 (m, 2H), 3.15 (d, J=6.5Hz, 2H), 2.35 - 2.53 (m, 2H), 1.99 - 2.12 (m, 1H), 1.50 - 1.95 (m, 4H)	A: 0.48 B: 0.25

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-35	52	amorphous	9.63 (d, J=2.6Hz, 1H), 7.09 - 7.42 (m, 8H), 6.03 - 6.25 (m, 1H), 4.62 - 4.82 (m, 2H), 3.37 - 3.51 (m, 1H), 3.19 (d, J=6.5Hz, 2H), 2.90 - 3.16 (m, 2H), 2.30 - 2.48 (m, 1H), 1.50 - 2.02 (m, 4H)	A: 0.36 B: 0.18
1-36	68	amorphous	9.66 (s, 1H), 7.10 - 7.58 (m, 8H), 5.98 - 6.14 (m, 1H), 4.79 (q, J=6.5Hz, 1H), 4.30 - 4.80 (m, 1H), 3.50 - 4.00 (m, 1H) 3.20 (d, J=6.5Hz, 2H), 2.75 - 3.20 (m, 2H), 2.40 (tt, J=10.9Hz, J=4.1Hz, 1H), 1.50 - 2.00 (m, 4H)	A: 0.23 B: 0.08
1-37	33	amorphous	9.63 (s, 1H), 7.20 - 7.36 (m, 3H), 7.09 - 7.17 (m, 2H), 6.08 - 6.26 (m, 1H), 4.74 (q, J=6.5Hz, 1H), 4.39 (d, J=13.3Hz, 2H), 3.19 (d, J=6.4Hz, 2H), 2.75 - 2.92 (m, 2H), 2.38 (tt, J=11.2Hz, J=4.1Hz, 1H), 1.50 - 1.90 (m, 4H), 1.27 (s, 9H)	A: 0.25 B: 0.09
1-38	53	amorphous	9.60 (s, 1H), 7.06 - 7.45 (m, 15H), 5.90 - 6.14 (m, 1H), 5.19 (s, 1H), 4.52 - 4.80 (m, 2H), 3.80 - 4.05 (m, 1H), 3.17 (d, J=6.4Hz, 2H), 2.55 - 3.10 (m, 2H), 2.28 (tt, J=11.2Hz, J=3.9Hz, 1H), 1.20 - 1.90 (m, 4H)	A: 0.35 B: 0.12
1-39	9.9	amorphous	9.56 (s, 1H), 6.95 - 7.87 (m, 13H), 5.85 - 6.15 (m, 1H), 5.06 (s, 1H), 4.48 - 4.72 (m, 2H), 3.13 (d, J=5.8Hz, 2H), 0.70 - 3.05 (m, 8H)	A: 0.26 B: 0.09
1-40	42	oil	9.62 (s, 1H), 7.10 - 7.35 (m, 5H), 6.20 - 6.45 (m, 1H), 4.67 - 4.83 (m, 1H), 4.40 - 4.64 (m, 1H), 3.65 - 3.98 (m, 1H) 3.18 (dd, J=6.7Hz, J=2.8Hz, 2H), 2.95 - 3.23 (m, 1H), 2.57 - 2.78 (m, 1H), 2.61 (s, 3H), 2.37 (tt, J=11.1Hz, J=4.0Hz, 1H), 2.30 - 2.53 (m, 1H), 1.50 - 1.95 (m, 3H)	A: 0.06 B: 0.04

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-41	12	152.7 to 156.3°C	9.62 (s, 1H), 6.95 - 7.45 (m, 10H), 6.35 - 6.53 (m, 1H), 6.00 - 6.28 (m, 1H), 4.77 (q, J=6.5Hz, 1H), 3.95 - 4.15 (m, 2H), 3.20 (d, J=6.4Hz, 2H), 2.83 - 3.04 (m, 2H), 2.35 (tt, J=11.1Hz, J=4.0Hz, 1H), 1.55 - 2.00 (m, 4H)	A: 0.22 B: 0.03
1-42	75	109.9 to 111.6°C	9.64 (s, 1H), 7.96 (d, J=15.6Hz, 1H), 7.51 - 7.65 (m, 1H), 7.10 - 7.50 (m, 8H) 6.84 (d, J=15.5Hz, 1H), 6.01 - 6.30 (m, 1H), 4.77 (q, J=6.5Hz, 1H), 3.90 - 4.90 (m, 2H), 3.20 (d, J=6.6Hz, 2H), 2.60 - 3.40 (m, 2H), 2.42 (tt, J=11.2Hz, J=4.0Hz, 1H), 1.60 - 2.10 (m, 4H)	A: 0.23 B: 0.07
1-43	70	115.2 to 120.7°C	9.65 (s, 1H), 7.58 (d, J=15.5Hz, 1H), 7.51 (s, 1H), 7.08 - 7.47 (m, 8H), 6.87 (d, J=15.5Hz, 1H), 5.97 - 6.23 (m, 1H), 4.78 (q, J=6.5Hz, 1H), 3.85 - 4.90 (m, 2H), 3.20 (d, J=6.5Hz, 2H), 2.65 - 3.40 (m, 2H), 2.41 (tt, J=11.0Hz, J=4.0Hz, 1H), 1.55 - 2.05 (m, 4H)	A: 0.20 B: 0.06
1-44	63	128.7 to 147.7°C	9.66 (s, 1H), 7.59 (d, J=15.5Hz, 1H), 7.09 - 7.50 (m, 9H), 6.84 (d, J=15.5Hz, 1H), 6.00 - 6.18 (m, 1H), 4.50 - 4.88 (m, 2H), 4.00 - 4.30 (m, 1H), 3.20 (d, J=6.5Hz, 2H), 3.04 - 3.40 (m, 1H), 2.68 - 3.00 (m, 1H), 2.41 (tt, J=11.2Hz, J=3.9Hz, 1H), 1.59 - 2.10 (m, 4H)	A: 0.16 B: 0.06
1-45	43	amorphous	9.56 (s, 1H), 7.80 - 7.90 (m, 4H), 7.45 - 7.55 (m, 2H), 7.46 (dd, J=5Hz, 1Hz, 1H), 6.40 - 6.50 (m, 1H), 4.50 - 4.90 (m, 1H), 4.52 (q, J=7Hz, 1H), 3.55 - 4.10 (m, 1H), 2.70 - 3.10 (m, 2H), 2.35 - 2.50 (m, 1H), 1.50 - 2.05 (m, 6H), 1.20 - 1.40 (m, 4H), 0.88 (t, J=6Hz, 3H)	A: 0.20 B: 0.07
1-46	38	amorphous	9.54 (s, 1H), 7.80 - 7.93 (m, 4H), 7.40 - 7.60 (m, 3H), 7.20 - 7.35 (m, 5H), 6.10 - 6.25 (m, 1H), 4.50 - 4.90 (m, 2H) 3.60 - 4.10 (m, 1H), 2.80 - 3.15 (m, 2H) 2.50 - 2.75 (m, 2H), 2.40 - 2.50 (m, 1H) 1.50 - 2.10 (m, 8H)	A: 0.20 B: 0.06

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-47	40	amorphous	9.54 (s, 1H), 7.80 - 7.90 (m, 4H), 7.40 - 7.60 (m, 3H), 7.00 - 7.30 (m, 5H), 6.20 - 6.30 (m, 1H), 4.50 - 4.85 (m, 1H) 4.54 (q, J=7Hz, 1H), 3.60 - 4.10 (m, 1H) 2.70 - 3.10 (m, 2H), 2.59 (t, J=7Hz, 2H) 2.35 - 2.50 (m, 1H), 1.50 - 2.05 (m, 8H) 1.20 - 1.45 (m, 2H)	A: 0.20 B: 0.07
1-48	6.4	amorphous	9.56 (s, 1H), 7.80 - 7.90 (m, 4H), 7.45 - 7.60 (m, 3H), 7.05 - 7.30 (m, 5H), 6.17 (d, J=7Hz, 1H), 4.55 - 4.90 (m, 1H) 4.57 (q, J=6Hz, 1H), 3.40 - 4.15 (m, 1H) 2.75 - 3.20 (m, 2H), 2.58 (t, J=8Hz, 2H) 2.35 - 2.55 (m, 1H), 1.50 - 2.10 (m, 8H) 1.25 - 1.50 (m, 4H)	A: 0.23 B: 0.09
1-49	19	amorphous	9.65 (s, 1H), 8.33 (bs, 1H), 7.80 - 7.95 (m, 4H), 7.50 - 7.65 (m, 3H), 7.44 (dd, J=8Hz, 1Hz, 1H), 7.36 (d, J=7Hz, 1H), 7.20 (t, J=7Hz, 1H), 7.13 (t, J=7Hz, 1H) 6.98 (d, J=0.5Hz, 1H), 6.22 (d, J=6Hz, 1H), 4.84 (q, J=7Hz, 1H), 4.40 - 4.80 (m, 1H), 3.50 - 4.10 (m, 1H), 3.40 (dd, J=15Hz, 5Hz, 1H), 3.30 (dd, J=15Hz, 6Hz, 1H), 2.90 - 3.10 (m, 2H), 2.30 - 2.40 (m, 1H), 1.50 - 2.00 (m, 4H)	A: 0.16 B: 0.02
1-50	8.4	amorphous	9.58 (s, 1H), 7.78 - 7.96 (m, 4H), 7.20 - 7.60 (m, 8H), 6.67 - 6.77 (m, 1H), 5.61 (d, J=6.0Hz, 1H), 4.30 - 5.00 (m, 1H), 3.60 - 4.20 (m, 1H), 2.80 - 3.23 (m, 2H), 2.53 (tt, J=11.1Hz, J=4.3Hz, 1H), 1.40 - 2.20 (m, 4H)	A: 0.30 B: 0.09
1-51	72	amorphous	9.51 (s, 1H), 7.80 - 7.93 (m, 4H), 7.13 - 7.58 (m, 7H), 6.45 - 6.61 (m, 1H), 4.50 - 4.60 (m, 1H), 4.40 - 4.90 (m, 1H) 3.82 (s, 2H), 3.60 - 4.10 (m, 1H), 2.80 - 3.15 (m, 2H), 2.36 - 2.65 (m, 3H), 2.17 - 2.34 (m, 1H), 1.55 - 2.05 (m, 5H)	A: 0.21 B: 0.07

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-52	30	amorphous	9.59 (s, 1H), 7.80 - 7.92 (m, 4H), 7.44 - 7.58 (m, 3H), 6.48 - 6.66 (m, 1H), 4.57 - 4.69 (m, 1H), 4.30 - 5.00 (m, 1H) 3.60 - 4.30 (m, 1H), 2.80 - 3.15 (m, 2H) 2.43 - 2.65 (m, 3H), 2.21 - 2.38 (m, 1H) 2.09 (s, 3H), 1.65 - 2.10 (m, 5H)	A: 0.16 B: 0.06
1-53	74	amorphous	9.64 (s, 1H), 7.80 - 7.95 (m, 4H), 7.22 - 7.60 (m, 8H), 7.03 (d, J=8.7Hz, 2H), 6.90 (d, J=8.6Hz, 2H), 6.04 - 6.18 (m, 1H), 5.03 (s, 2H), 4.68 - 4.82 (m, 1H), 4.40 - 4.85 (m, 1H), 3.55 - 4.25 (m, 1H) 3.14 (d, J=6.4Hz, 2H), 2.75 - 3.20 (m, 2H), 2.32 - 2.48 (m, 1H), 1.40 - 2.00 (m, 4H)	A: 0.20 B: 0.06
1-54	52	amorphous	9.51 (s, 1H), 7.80 - 7.93 (m, 4H), 7.45 - 7.59 (m, 3H), 7.20 - 7.35 (m, 4H), 6.30 - 6.50 (m, 1H), 4.56 - 4.70 (m, 1H) 4.35 - 4.95 (m, 1H), 3.74 - 4.33 (m, 1H) 3.70 (s, 2H), 2.91 (d, J=5.9Hz, 2H), 2.80 - 3.18 (m, 2H), 2.38 - 2.51 (m, 1H) 1.50 - 2.10 (m, 4H)	A: 0.18 B: 0.05
1-55	68	amorphous	9.64 (d, J=1.9Hz, 1H), 7.80 - 7.93 (m, 4H), 7.40 - 7.60 (m, 3H), 6.95 - 7.32 (m, 4H), 6.15 - 6.37 (m, 1H), 4.70 - 4.82 (m, 1H), 4.50 - 4.85 (m, 1H), 3.90 - 4.10 (m, 1H), 3.13 - 3.35 (m, 2H), 2.75 - 3.14 (m, 2H), 2.33 - 2.46 (m, 1H) 1.50 - 2.10 (m, 4H)	A: 0.22 B: 0.07
1-56	18	104.5 to 137.7°C	9.61 (s, 1H), 8.32 (s, 1H), 8.08 (bs, 1H), 7.90 - 8.10 (m, 3H), 7.55 - 7.80 (m, 3H), 7.54 (d, J=8Hz, 1H), 7.35 (d, J=8Hz, 1H), 7.20 (t, J=7Hz, 1H), 7.10 (t, J=8Hz, 1H), 6.96 (d, J=2Hz, 1H), 5.95 - 6.10 (m, 1H), 4.80 (q, J=5Hz, 1H) 3.75 - 4.90 (m, 2H), 3.38 (dd, J=15Hz, 5Hz, 1H), 3.25 (dd, J=15Hz, 7Hz, 1H), 2.30 - 2.50 (m, 2H), 1.90 - 2.05 (m, 1H) 1.60 - 1.90 (m, 4H)	A: 0.45 B: 0.14

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-57	3.5	amorphous	9.66 (s, 1H), 8.16 (bs, 1H), 7.64 (d, J=15Hz, 1H), 7.05 - 7.60 (m, 9H), 7.02 (d, J=2Hz, 1H), 6.85 (d, J=15Hz, 1H), 6.10 - 6.20 (m, 1H), 4.86 (q, J=5Hz, 1H), 4.40 - 4.80 (m, 1H), 3.90 - 4.30 (m, 1H), 3.43 (dd, J=14Hz, 5Hz, 1H), 3.30 (dd, J=14Hz, 1H), 2.60 - 3.30 (m, 2H), 2.37 (tt, J=8Hz, 3Hz, 1H), 1.50 - 1.90 (m, 4H)	A: 0.13 B: 0.02
1-58	20	171.3 to 172.0°C	9.63 (s, 1H), 8.19 (bs, 1H), 7.95 (d, J=15Hz, 1H), 7.56 - 7.60 (m, 2H), 7.35 - 7.45 (m, 2H), 7.11 - 7.30 (m, 4H), 7.01 (d, J=2Hz, 1H), 6.83 (d, J=15Hz, 1H), 6.15 - 6.30 (m, 1H), 4.85 (q, J=6Hz, 1H) 3.85 - 4.85 (m, 2H), 3.41 (dd, J=15Hz, 6Hz, 1H), 3.30 (dd, J=15Hz, 7Hz, 1H), 2.50 - 3.30 (m, 2H), 2.37 (tt, J=10Hz, 3Hz, 1H), 1.40 - 1.95 (m, 4H)	A: 0.17 B: 0.03
1-59	82	114.1 to 118.9°C	9.65 (s, 1H), 7.97 (d, J=15.5Hz, 1H), 7.20 - 7.65 (m, 9H), 7.03 (d, J=8.7Hz, 2H), 6.91 (d, J=8.7Hz, 2H), 6.85 (d, J=15.5Hz, 1H), 5.95 - 6.11 (m, 1H), 5.04 (s, 2H), 4.50 - 4.81 (m, 2H), 3.95 - 4.24 (m, 1H), 3.14 (d, J=6.8Hz, 2H), 2.65 - 3.30 (m, 2H), 2.41 (tt, J=11.1Hz, J=3.8Hz, 1H), 1.50 - 1.95 (m, 4H)	A: 0.23 B: 0.05
1-60	58	137.2 to 176.2°C	9.58 (s, 1H), 8.33 (s, 1H), 7.85 - 8.05 (m, 3H), 7.55 - 7.80 (m, 3H), 7.25 - 7.50 (m, 5H), 6.97 (d, J=8.5Hz, 2H), 6.86 (d, J=8.6Hz, 2H), 5.86 - 6.05 (m, 1H), 5.02 (s, 2H), 4.60 - 4.72 (m, 1H), 3.75 - 3.93 (m, 2H), 3.08 (d, J=6.4Hz, 2H), 2.34 - 2.54 (m, 2H), 1.70 - 2.10 (m, 5H)	A: 0.53 B: 0.24
1-61	61	133.2 to 135.8°C	9.64 (s, 1H), 7.65 (d, J=15.5Hz, 1H), 7.30 - 7.58 (m, 10H), 7.03 (d, J=8.6Hz, 2H), 6.91 (d, J=8.7Hz, 2H), 6.87 (d, J=15.4Hz, 1H), 6.00 - 6.18 (m, 1H), 5.04 (s, 2H), 3.90 - 4.90 (m, 3H), 3.14 (d, J=6.4Hz, 2H), 2.60 - 3.40 (m, 2H), 2.41 (tt, J=11.1Hz, J=3.9Hz, 1H), 1.50 - 2.10 (m, 4H)	A: 0.20 B: 0.04

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-62	0.58	amorphous	9.55 (s, 1H), 7.97 (d, J=15.6Hz, 1H), 7.53 - 7.64 (m, 1H), 7.19 - 7.45 (m, 7H) 6.86 (d, J=15.6Hz, 1H), 6.25 - 6.45 (m, 1H), 3.90 - 4.85 (m, 3H), 3.66 (s, 2H), 2.60 - 3.37 (m, 2H), 2.15 - 2.55 (m, 4H) 1.60 - 2.04 (m, 5H)	A: 0.23 B: 0.06
1-63	64	amorphous	9.51 (s, 1H), 8.34 (s, 1H), 7.90 - 8.03 (m, 3H), 7.59 - 7.79 (m, 3H), 7.15 - 7.22 (m, 4H), 6.00 - 6.17 (m, 1H), 4.46 - 4.55 (m, 1H), 3.79 - 3.95 (m, 2H), 3.62 (s, 2H), 1.60 - 2.55 (m, 11H)	A: 0.54 B: 0.25
1-64	19	amorphous	9.54 (s, 1H), 8.31 (s, 1H), 7.85 - 8.00 (m, 3H), 7.55 - 7.85 (m, 3H), 7.17 (d, J=9Hz, 2H), 6.74 (d, J=9Hz, 2H), 6.20 - 6.35 (m, 1H), 4.45 - 4.60 (m, 1H), 3.70 3.95 (m, 4H), 2.30 - 2.50 (m, 2H), 2.00 - 2.20 (m, 2H), 1.60 - 2.00 (m, 7H)	A: 0.45 B: 0.23
1-65	64	107.6 to 117.6°C	9.52 (s, 1H), 8.35 (s, 1H), 7.80 - 8.10 (m, 3H), 7.55 - 7.80 (m, 3H), 7.20 - 7.30 (m, 4H), 5.96 (d, J=6Hz, 1H), 4.55 (q, J=5Hz, 1H), 3.80 - 3.90 (m, 2H), 2.75 - 2.90 (m, 2H), 2.40 - 2.50 (m, 1H), 2.00 - 2.10 (m, 1H), 1.40 - 1.90 (m, 7H)	A: 0.47 B: 0.24
1-66	20	amorphous	9.60 (s, 1H), 7.95 (d, J=15Hz, 1H), 7.55 - 7.62 (m, 1H), 7.35 - 7.45 (m, 1H), 7.15 - 7.35 (m, 4H), 6.85 (d, J=15Hz, 1H), 6.70 - 6.85 (m, 2H), 6.35 - 6.45 (m, 1H), 4.55 - 4.80 (m, 2H), 4.00 - 4.25 (m, 1H), 3.85 - 4.00 (m, 2H), 3.00 - 3.30 (m, 1H), 2.70 - 3.00 (m, 1H), 2.48 (tt, J=8Hz, 4Hz, 1H), 2.10 - 2.30 (m, 1H), 1.65 - 2.00 (m, 7H)	A: 0.17 B: 0.05
1-67	52	147.8 to 151.5°C	9.56 (s, 1H), 7.97 (d, J=15Hz, 1H), 7.55 - 7.65 (m, 2H), 7.35 - 7.45 (m, 2H), 7.20 - 7.40 (m, 4H), 6.85 (d, J=15Hz, 1H), 6.10 (d, J=7Hz, 1H), 4.55 - 4.80 (m, 1H), 4.59 (q, J=5Hz, 1H), 4.05 - 4.20 (m, 1H), 3.10 - 3.30 (m, 1H), 2.70 - 3.05 (m, 3H), 2.35 - 2.50 (m, 1H), 2.05 - 2.25 (m, 1H), 1.60 - 2.00 (m, 7H)	A: 0.19 B: 0.05

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-68	37	amorphous	9.63 (s, 1H), 8.33 (s, 1H), 7.96 (d, J=15Hz, 2H), 7.92 (dd, J=9Hz, J=1Hz, 1H), 7.73 (dd, J=9Hz, J=1Hz, 1H), 7.60 - 7.69 (m, 2H), 7.26 (t, J=7Hz, 1H), 6.96 (t, J=7Hz, 1H), 6.79 (d, J=8Hz, 2H), 6.37 - 6.42 (m, 1H), 4.56 (q, J=5Hz, 1H), 4.00 4.09 (m, 1H), 3.82 - 3.92 (m, 3H), 2.22 2.48 (m, 4H), 2.04 - 2.18 (m, 1H), 1.77 - 1.94 (m, 4H)	A: 0.47 B: 0.20
1-69	40	amorphous	9.53 (s, 1H), 8.34 (s, 1H), 7.99 (d, J=8Hz, 2H), 7.93 (d, J=7Hz, J=1Hz, 1H), 7.75 (dd, J=10Hz, J=2Hz, 1H), 7.60 - 7.70 (m, 2H), 7.21 - 7.28 (m, 4H), 6.11 - 6.18 (m, 1H), 4.59 (t, J=5Hz, 1H), 3.82 - 3.91 (m, 2H), 2.78 - 2.98 (m, 2H) 2.42 - 2.52 (m, 2H), 2.25 - 2.37 (m, 2H) 2.04 - 2.16 (m, 1H), 1.82 - 1.96 (m, 4H)	A: 0.47 B: 0.20
1-70	37	amorphous	9.69 (s, 1H), 7.96 (d, J=15Hz, 1H), 7.57 - 7.60 (m, 1H), 7.39 - 7.42 (m, 1H), 7.21 - 7.31 (m, 4H), 6.97 (t, J=7Hz, 1H) 6.73 - 6.87 (m, 2H), 6.48 - 6.52 (m, 1H), 4.57 - 4.72 (m, 2H), 4.02 - 4.14 (m, 2H), 3.88 - 3.98 (m, 1H), 3.10 - 3.24 (m, 1H), 2.75 - 2.90 (m, 1H), 2.40 - 2.57 (m, 3H), 1.89 - 1.97 (m, 2H), 1.62 - 1.82 (m, 2H)	A: 0.19 B: 0.06
1-71	50	amorphous	9.57 (s, 1H), 7.97 (d, J=16Hz, 1H), 7.56 - 7.59 (m, 1H), 7.40 - 7.42 (m, 1H), 7.23 - 7.29 (m, 6H), 6.85 (t, J=16Hz, 1H), 6.40 - 6.47 (m, 1H), 4.63 (q, J=7Hz, 1H), 4.61 - 4.71 (m, 1H), 4.10 - 4.20 (m, 1H), 3.10 - 3.30 (m, 1H), 2.85 - 3.03 (m, 2H), 2.75 - 2.95 (m, 1H), 2.45 - 2.54 (m, 1H), 2.28 - 2.39 (m, 1H) 1.89 - 2.01 (m, 3H), 1.67 - 1.82 (m, 2H)	A: 0.18 B: 0.04

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-72	65	amorphous	9.66 (s, 1H), 8.26 (d, J=9Hz, 1H), 8.15 (d, J=9Hz, 1H), 7.86 (d, J=8Hz, 1H), 7.76 (t, J=7Hz, 1H), 6.67 (dd, J=8Hz, 1Hz, 1H), 7.60 (t, J=8Hz, 1H), 7.10 - 7.35 (m, 5H), 6.14 (m, 1H), 4.65 - 4.85 (m, 2H), 4.00 - 4.15 (m, 1H), 3.19 (d, J=6Hz, 2H), 3.10 - 3.25 (m, 1H), 2.85 - 3.00 (m, 1H), 2.40 - 2.50 (m, 1H), 1.70 - 2.00 (m, 4H)	A: 0.10 B: 0.02
1-73	69	amorphous	9.67 (s, 1H), 8.91 (d, J=2Hz, 1H), 8.29 (brs, 1H), 8.23 (d, J=2Hz, 1H), 8.15 (d, J=8Hz, 1H), 7.87 (d, J=8Hz, 1H), 7.80 (td, J=8Hz, 1Hz, 1H), 7.55 - 7.65 (m, 2H), 7.37 (d, J=8Hz, 1H), 7.05 - 7.30 (m, 2H), 7.00 (d, J=2Hz, 1H), 6.17 (d, J=6Hz, 1H), 4.80 - 4.90 (m, 1H), 4.50 - 4.80 (m, 1H), 3.60 - 3.90 (m, 1H) 3.45 (dd, J=15Hz, 5Hz, 1H), 3.30 (dd, J=15Hz, 7Hz, 1H), 2.80 - 3.20 (m, 2H), 2.30 - 2.45 (m, 1H), 1.60 - 1.90 (m, 4H)	A: 0.04 B: 0.01
1-74	20	amorphous	9.65 (s, 1H), 9.22 (s, 1H), 8.05 (s, 1H) 8.02 (d, J=8Hz, 1H), 7.90 (d, J=8Hz, 1H) 7.65 - 7.80 (m, 2H), 7.20 - 7.50 (m, 5H) 7.05 (d, J=8Hz, 2H), 6.90 (d, J=8Hz, 2H) 6.05 (d, J=6Hz, 1H), 5.03 (s, 2H), 4.90 - 5.05 (m, 1H), 4.70 - 4.85 (m, 2H) 3.15 (d, J=6Hz, 2H), 2.85 - 3.30 (m, 2H) 2.35 - 2.50 (m, 1H), 1.60 - 1.90 (m, 4H)	A: 0.05 B: 0.01
1-75	34	amorphous	9.66 (s, 1H), 7.10 - 7.70 (m, 14H), 6.05 (d, J=6Hz, 1H), 4.50 - 4.85 (m, 2H), 3.75 - 4.05 (m, 1H), 3.20 (d, J=6Hz, 2H) 2.70 - 3.10 (m, 2H), 2.30 - 2.50 (m, 1H) 1.60 - 1.95 (m, 4H)	A: 0.18 B: 0.04

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-76	61	amorphous	9.65 (s, 1H), 8.76 (s, 1H), 8.57 (d, J=3Hz, 1H), 7.82 (d, J=8Hz, 1H), 7.63 (d, J=15Hz, 1H), 7.30 - 7.45 (m, 6H), 6.80 - 7.10 (m, 5H), 6.04 (d, J=6Hz, 1H), 5.04 (s, 2H), 4.55 - 4.80 (m, 2H), 4.05 - 4.20 (m, 1H), 3.10 - 3.30 (m, 1H), 3.14 (d, J=6Hz, 2H), 2.75 - 2.90 (m, 1H), 2.41 (tt, J=11Hz, 4Hz, 1H), 1.60 - 2.00 (m, 4H)	A: 0.02 B: 0.01
1-77	59	amorphous	9.65 (s, 1H), 7.78 (d, J=15Hz, 1H), 7.20 - 7.50 (m, 6H), 7.00 - 7.10 (m, 3H), 6.90 (d, J=8Hz, 2H), 6.67 (d, J=15Hz, 1H), 5.99 (d, J=6Hz, 1H), 5.04 (s, 2H), 4.55 - 4.80 (m, 2H), 3.95 - 4.25 (m, 1H) 3.00 - 3.20 (m, 1H), 3.14 (d, J=6Hz, 2H) 2.70 - 2.95 (m, 1H), 2.39 (tt, 11Hz, 4Hz, 1H), 1.50 - 1.95 (m, 4H)	A: 0.18 B: 0.04
1-78	10	amorphous	9.68 (s, 1H), 8.37 (s, 1H), 8.02 (d, J=8Hz, 1H), 7.84 (d, J=15Hz, 1H), 7.45 - 7.70 (m, 4H), 7.36 (d, J=8Hz, 1H), 7.00 - 7.25 (m, 3H), 6.66 (d, J=15Hz, 1H), 5.97 (d, J=7Hz, 1H), 4.80 - 4.90 (m, 1H) 4.40 - 4.65 (m, 1H), 4.00 - 4.15 (m, 1H) 3.00 - 3.20 (m, 3H), 2.65 - 2.90 (m, 1H) 2.25 - 2.35 (m, 1H), 1.50 - 1.80 (m, 4H)	A: 0.03 B: 0.02
1-79	15	amorphous	9.64 (s, 1H), 8.24 (s, 1H), 7.60 (d, J=8Hz, 1H), 7.05 - 7.42 (m, 8H), 7.00 (d, J=2Hz, 1H), 6.51 (s, 1H), 6.15 - 6.30 (m, 1H), 4.80 - 4.90 (m, 1H), 3.85 - 4.55 (m, 2H), 3.45 (dd, J=15Hz, 5Hz, 1H) 3.30 (dd, J=15Hz, 8Hz, 1H), 2.70 - 3.10 (m, 2H), 2.35 (tt, J=11Hz, 3Hz, 1H), 2.08 (s, 3H), 1.60 - 1.90 (m, 4H)	A: 0.05 B: 0.03

Table 9

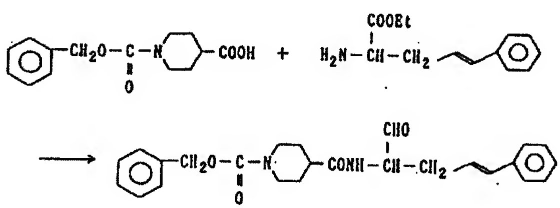
Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-80	25	amorphous	9.61 (s, 1H), 9.04 (dd, J=4Hz, 1Hz, 1H) 8.47 (dd, J=8Hz, 1Hz, 1H), 8.23 (dd, J=8Hz, 1Hz, 1H), 8.03 (d, J=8Hz, 1H), 7.61 (t, J=7Hz, 1H), 7.50 - 7.60 (m, 1H), 7.05 - 7.40 (m, 5H), 5.95 (d, J=6Hz, 1H) 4.65 - 4.75 (m, 1H), 4.00 - 4.20 (m, 2H) 3.15 (d, J=6Hz, 2H), 2.80 - 3.00 (m, 2H) 2.10 - 2.20 (m, 1H), 1.60 - 1.90 (m, 4H)	A: 0.28 B: 0.09
1-81	71	amorphous	9.60 - 9.70 (m, 1H), 7.00 - 7.43 (m, 15H), 5.60 - 6.00 (m, 2H), 4.98 - 5.16 (m, 2H), 4.80 - 4.98 (m, 1H), 4.67 - 4.80 (m, 1H), 4.40 - 4.55 (m, 1H), 3.50 - 3.77 (m, 1H), 3.10 - 3.25 (m, 2H), 2.80 - 3.10 (m, 2H), 2.49 - 2.68 (m, 1H) 1.20 - 2.35 (m, 6H)	A: 0.30 B: 0.07
1-82	69	amorphous	9.60 - 9.70 (m, 1H), 7.02 - 7.43 (m, 15H), 5.60 - 6.00 (m, 2H), 4.99 - 5.15 (m, 2H), 4.80 - 4.96 (m, 1H), 4.65 - 4.80 (m, 1H), 4.35 - 4.45 (m, 1H), 3.53 - 3.75 (m, 1H), 3.10 - 3.27 (m, 2H), 2.84 - 3.10 (m, 2H), 2.48 - 2.68 (m, 1H) 1.20 - 2.40 (m, 6H)	A: 0.30 B: 0.07
1-83	88	174.0 - 176.0	9.67 (s, 1H), 9.41 (s, 1H), 7.64 (d, J=8Hz, 1H), 7.43 (d, J=8Hz, 1H), 7.08 - 7.50 (m, 7H), 6.75 (d, J=2Hz, 1H), 6.05 - 6.30 (m, 1H), 4.75 - 4.87 (m, 1H), 4.53 - 4.74 (m, 2H), 3.20 (d, J=6Hz, 2H) 2.90 - 3.40 (m, 2H), 2.43 (tt, J=11Hz, J=4Hz, 1H), 1.50 - 2.05 (m, 4H)	A: 0.21 B: 0.04
1-84	73	amorphous	9.74 (s, 1H), 9.62 (s, 1H), 7.55 - 7.75 (m, 1H), 7.00 - 7.45 (m, 9H), 6.41 (d, J=7Hz, 1H), 4.64 - 4.80 (m, 1H), 4.15 - 4.50 (m, 2H), 3.05 - 3.35 (m, 2H), 2.75 - 3.05 (m, 2H), 1.50 - 2.45 (m, 5H)	A: 0.06 B: 0.01

Table 9

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-85	87	183.0 - 184.8	9.65 (s, 1H), 7.23 - 8.00 (m, 13H), 7.03 (d, J=9Hz, 2H), 6.99 (d, J=16Hz, 1H), 6.91 (d, J=9Hz, 2H), 5.97 - 6.13 (m, 1H) 5.04 (s, 2H), 4.70 - 4.83 (m, 1H), 4.00 - 4.85 (m, 2H), 3.15 (d, J=7Hz, 2H), 2.60 - 3.40 (m, 2H), 2.42 (tt, J=11Hz, J=4Hz, 1H), 1.50 - 2.00 (m, 4H)	A: 0.17 B: 0.04
1-86	72	105.5 - 109.3	9.64 (s, 1H), 7.08 - 7.45 (m, 10H), 5.92 - 6.08 (m, 1H), 4.73 (q, J=7Hz, 1H), 3.40 - 3.65 (m, 2H), 3.18 (d, J=6Hz, 2H) 2.83 - 3.04 (m, 2H), 1.50 - 2.30 (m, 7H)	A: 0.11 B: 0.02
1-87	20	amorphous	9.64 (s, 1H), 7.05 - 7.90 (m, 12H), 5.90 - 6.10 (m, 1H), 4.69 - 4.80 (m, 1H), 3.66 (s, 2H), 3.18 (d, J=6Hz, 2H), 2.85 - 3.05 (m, 2H), 1.50 - 2.25 (m, 7H)	A: 0.10 B: 0.02
1-88	54	amorphous	9.62 (s, 1H), 8.24 (s, 1H), 6.90 - 7.90 (m, 12H), 6.14 (d, J=7Hz, 1H), 4.74 - 4.87 (m, 1H), 3.63 (s, 2H), 3.20 - 3.48 (m, 2H), 2.80 - 3.05 (m, 2H), 1.60 - 2.25 (m, 7H)	A: 0.10 B: 0.01
1-89	35	amorphous	9.65 (s, 1H), 7.05 - 7.47 (m, 8H), 5.90 - 6.10 (m, 1H), 4.69 - 4.82 (m, 1H), 3.35 - 3.60 (m, 2H), 3.19 (d, J=6Hz, 2H), 2.75 - 3.00 (m, 2H), 1.50 - 2.25 (m, 7H)	A: 0.17 B: 0.05
1-90	89	amorphous	9.63 (s, 1H), 7.19 - 7.50 (m, 10H), 7.03 (d, J=9Hz, 2H), 6.90 (d, J=9Hz, 2H), 6.51 (d, J=16Hz, 1H), 6.27 (td, J=7Hz, J=16Hz, 1H), 6.00 (d, J=6Hz, 1H), 5.03 (s, 2H), 4.65 - 4.75 (m, 1H), 2.90 - 3.25 (m, 6H), 2.14 (tt, J=11Hz, J=4Hz, 1H), 1.92 - 2.08 (m, 2H), 1.60 - 2.91 (m, 4H)	A: 0.05 B: 0.01

Example 1-91

Synthesis of 1-benzyloxycarbonyl-piperidine-4-carboxylic acid-(1R,1S)-(1-formyl-4-phenyl)-3-butenylamide (Compound No. 1-91):



0.70 ml (4.97 mmol) of triethylamine and 1.14 g (5.96 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride were successively added to 50 ml of a dichloromethane solution containing 1.31 g (4.97 mmol) of 1-benzyloxycarbonylpiperidine-4-carboxylic acid synthesized in Reference Example 1-4 and 1.27 g (4.97 mmol) of (2R,2S)-2-amino-5-phenyl-4-pentanoic acid ethyl ester hydrochloride (Compound No. 1-67) synthesized in Reference Example 1-67 under an ice-cooled condition. After stirring overnight at room temperature, the solvent was distilled away from the reaction mixture under reduced pressure and the residue thus obtained was dissolved in ethyl acetate. This solution was washed successively with a 1 N hydrochloric acid solution, a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled away under reduced pressure, the residue thus obtained was separated with chromatograph, whereby 1.65 g of 1-benzyloxycarbonyl-piperidine-4-carboxylic acid-(2R,2S)-(1-ethoxycarbonyl-1-cinnamyl)methylamide was obtained in a yield of 71%.

1.65 g (3.55 mmol) of the above prepared compound was dissolved in 30 ml of tetrahydrofuran. 0.193 g (8.88 mmol) of lithium boron hydride was added to the tetrahydrofuran solution in an ice bath, followed by dropping of a mixture of 4.5 ml of methanol and 5.5 ml of tetrahydrofuran. After stirring for two hours, 20 ml of water was further added to the reaction mixture and tetrahydrofuran was distilled away therefrom under reduced pressure. With the addition of ice and 1 N hydrochloric acid to the residue, the mixture was extracted with ethyl acetate. The resultant organic extract layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. 1.35 g (3.20 mmol) of the residue thus obtained was made acid with the addition of pyridine•sulfur trioxide complex in dimethyl sulfoxide in accordance with the same procedure as in Example 1-1, whereby 0.9 g of the captioned Compound No. 1-91 was obtained as an oily material in a yield of 43%.

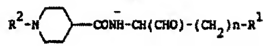
NMR (δ, $CDCl_3$): 9.65 (s, 1H), 7.15 - 7.45 (m, 10H), 6.47 (d, J=15.7Hz, 1H), 6.06 - 6.18 (m, 1H), 5.95 - 6.10 (m, 1H), 5.16 (s, 2H), 4.65 - 4.75 (m, 1H), 4.02 - 4.35 (m, 2H), 2.67 - 2.95 (m, 4H), 2.33 (tt, J=11.3Hz, J=3.9Hz, 1H), 1.50 - 1.98 (m, 4H)

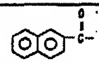
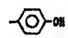
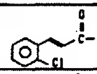
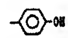
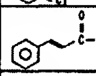
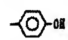
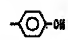
Examples 1-92 to 1-95

The same reaction procedure as in Example 1-91 was repeated except that the carboxylic acid derivative (the compound synthesized in Reference Example 1-4) and the amine derivative (Reference Compound No. 1-67 synthesized in Reference Example 1-67) used in Example 1-91 were respectively replaced by a carboxylic acid derivative (Material 1) and an amine derivative (Material 2) shown in Table 10, whereby Compounds No. 1-92 to No. 1-95 (cyclic carboxylic acid amide derivative) shown in Table 10 were respectively obtained.

Table 11 shows the yield, melting point or state, the NMR analysis data and the R_f values obtained by TLC analysis of each cylic carboxylic acid amide derivative. The developing solvent A used in the TLC analysis is ethyl acetate and the developing solvent B is a mixture of methylene chloride and acetone at a mixing ratio of 10:1.

Table 10



Ex.	Material 1 (*)	Material 2	R^2	n	R^1	Compound
1-92	1-12	L-tyrosine-ethylester		1		1-(2-naphthoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-hydroxyphenyl)]ethylamide
1-93	1-18	L-tyrosine-ethylester		1		1-(2-chlorocinnamoyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-hydroxyphenyl)]ethylamide
1-94	1-10	L-tyrosine-ethylester		1		1-cinnamoylpiperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-hydroxyphenyl)]ethylamide
1-95	1-30	L-tyrosine-ethylester		1		1-(2-naphthylsulfonyl)piperidine-4-carboxylic acid-(1S)-[1-formyl-2-(4-hydroxyphenyl)]ethylamide

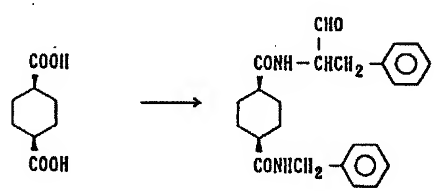
(*) Each material is indicated by the Reference Reference Example Number in which it is synthesized.

Table 11

Ex.	Yield	Melting Point (°C) or State	NMR (δ, $CDCl_3$)	R_f Values
1-92	37	amorphous	9.58 (s, 1H), 7.77 - 7.93 (m, 4H), 7.32 - 7.60 (m, 3H), 6.93 (d, J=8.4Hz, 2H), 6.76 (d, J=8.4Hz, 2H), 6.30 - 6.58 (m, 1H), 4.30 - 4.83 (m, 2H), 3.55 - 4.10 (m, 1H), 2.60 - 3.22 (m, 4H), 2.30 - 2.48 (m, 1H), 1.50 - 2.00 (m, 4H)	A: 0.16 B: 0.02
1-93	45	166.6 to 178.2°C	9.64 (s, 1H), 7.97 (d, J=15.6Hz, 1H), 7.20 - 7.65 (m, 4H), 6.97 (d, J=8.4Hz, 2H), 6.85 (d, J=15.5Hz, 1H), 6.78 (d, J=8.3Hz, 2H), 6.02 - 6.17 (m, 1H), 3.90 - 4.90 (m, 3H), 3.13 (d, J=6.4Hz, 2H), 2.55 - 3.30 (m, 2H), 2.30 - 2.50 (m, 1H) 1.35 - 1.95 (m, 4H)	A: 0.18 B: 0.02
1-94	30	amorphous	9.62 (s, 1H), 7.63 (d, J=15.4Hz, 1H), 7.30 - 7.58 (m, 5H), 6.94 (d, J=8.5Hz, 2H), 6.86 (d, J=15.4Hz, 1H), 6.79 (d, J=8.4Hz, 2H), 6.20 - 6.50 (m, 1H), 3.95 - 4.85 (m, 3H), 2.57 - 3.30 (m, 4H), 2.35 - 2.51 (m, 1H), 1.50 - 1.95 (m, 4H)	A: 0.15 B: 0.01
1-95	64	130.3 to 158.6°C	9.57 (s, 1H), 8.33 (s, 1H), 7.88 - 8.04 (m, 3H), 7.59 - 7.78 (m, 3H), 6.92 (d, J=8.4Hz, 2H), 6.73 (d, J=8.6Hz, 2H), 5.90 - 6.12 (m, 1H), 4.62 - 4.73 (m, 1H) 3.75 - 3.90 (m, 2H), 3.07 (d, J=6.4Hz, 2H), 2.33 - 2.48 (m, 2H), 1.98 - 2.13 (m, 1H), 1.65 - 1.95 (m, 4H)	A: 0.49 B: 0.09

Example 1-96

Synthesis of cis-1-(N-benzylcarbamoyl)cyclohexane-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide (Compound No. 1-96):



To 200 ml of a chloroform solution containing 3.0 g (17.4 mmol) of commercially available cis-cyclohexane-1,4-dicarboxylic acid and 5.32 g (34.8 mmol) of N-hydroxybenzotriazole hydrate, 100 ml of a chloroform solution of 7.18 g (34.8 mmol) of dicyclohexylcarbodiimide was added dropwise under an ice-cooled condition. After stirring for 1 hour, 50 ml of a chloroform solution containing 2.83 g (17.4 mmol) of

(2S)-2-amino-3-phenylpropanol synthesized in Reference Example 1-48 and 1.76 g (17.4 mmol) of triethylamine was added dropwise to the above prepared reaction mixture. The reaction mixture was heated to room temperature and then stirred overnight.

Insoluble components were removed from the reaction mixture by filtration. The filtrate was washed with 1 N hydrochloric acid and extracted with 100 ml of a 1 N sodium hydroxide solution twice. The resulting water layer was made acid (pH=1) with the addition of concentrated hydrochloric acid thereto. The water layer was extracted with chloroform twice. The resultant organic extract layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure.

To 100 ml of a chloroform solution containing the above obtained residue and 0.857 g (8 mmol) of benzylamine, 0.958 g (5 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was added, and the reaction mixture was stirred overnight. The reaction mixture was washed successively with 1 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate, and a saturated aqueous solution of sodium chloride. The reaction mixture was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.2 g of cis-1-(N-benzylcarbamoyl)cyclohexanecarboxylicacid-(1S)-(1-hydroxymethyl-2-phenyl)ethylamide was obtained in a yield of 2.9% from the cis-cyclohexane-1,4-dicarboxylic acid.

NMR (δ, $CDCl_3$): 7.15 - 7.40 (m, 10H), 5.85 - 6.10 (m, 2H), 4.42 (d, J=6Hz, 2H), 4.10 - 4.25 (m, 1H), 3.67 (dd, J=11Hz, 3Hz, 1H), 3.56 (dd, J=11Hz, 5Hz, 1H), 2.80 - 2.95 (m, 2H), 2.67 (bs, 1H), 2.20 - 2.40 (m, 2H), 1.50 - 2.10 (m, 8H)

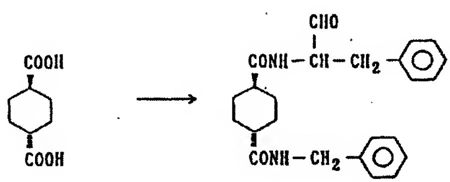
0.2 g (0.5 mmol) of the above prepared amide was made acid with pyridine•sulfur trioxide complex in dimethyl sulfoxide in accordance with the same procedure as in Example 1-1, whereby 0.18 g of the captioned Compound No. 1-96 was obtained as an oily material in a yield of 91%.

NMR (δ, $CDCl_3$): 9.58 (s, 1H), 7.10 - 7.40 (m, 10H), 6.10 - 6.30 (m, 1H), 5.80 - 6.00 (m, 1H), 4.69 (q, J=7Hz, 1H), 4.43 (d, J=5Hz, 2H), 3.15 (d, J=7Hz, 2H), 2.20 - 2.40 (m, 2H), 1.50 - 2.20 (m, 8H)

R_f values: 0.33 (Developing Solvent A)
0.04 (Developing Solvent B)

Example 1-97

Synthesis of trans-1-(N-benzylcarbamoyl)cyclohexane-4-carboxylic acid-(1S)-(1-formyl-2-phenyl)ethylamide (Compound No. 1-97):



The same reaction procedure as in Example 1-96 was repeated except that the cis-cyclohexane-1,4-didicarboxylic acid used in Example 1-96 was replaced by trans-cyclohexane-1,4-carboxylic acid, whereby trans-1-(N-benzylcarbamoyl)cyclohexane-carboxylic acid-(1S)-(1-hydroxymethyl-2-phenyl)ethylamide was obtained.

NMR (δ, $CDCl_3$): 7.10 - 7.35 (m, 10H), 4.30 - 4.40 (m, 2H), 4.05 - 4.20 (m, 1H), 3.51 (d, J=5Hz, 1H), 3.10 (d, J=5Hz, 1H), 2.85 - 3.00 (m, 1H), 2.60 - 2.75 (m, 1H), 2.05 - 2.35 (m, 2H), 1.70 - 2.00 (m, 4H), 1.25 - 1.70 (m, 4H)

The above prepared amide was made acid with pyridine•sulfur trioxide complex in ditrimethyl sulfoxide in accordance with the same procedure as in Example 1-1, whereby the captioned Compound No. 1-97 was obtained as white crystals.

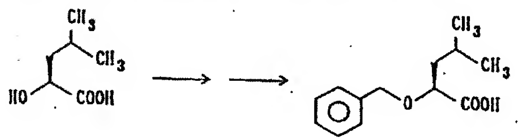
Melting point (°C): 174.9 - 180.7 (dec.)

NMR (δ, $CDCl_3$): 9.81 (s, 1H), 7.05 - 7.41 (m, 10H), 6.13 (d, J=8Hz, 1H), 5.80 - 6.05 (m, 1H), 4.67 (q, J=6Hz, 1H), 4.30 - 4.45 (m, 2H), 3.15 (d, J=6Hz, 2H), 2.05 - 2.20 (m, 2H), 1.70 - 2.00 (m, 4H), 1.40 - 1.60 (m, 4H)

R_f values: 0.14 (Developing Solvent A)
0.02 (Developing Solvent B)

Reference Example 2-1

Synthesis of (2S)-2-benzyloxy-4-methylpentanoic acid (Reference Compound No. 2-1):

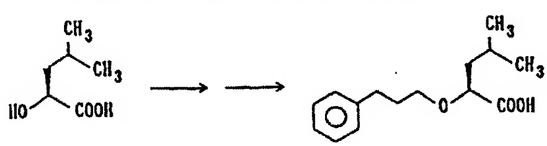


To 40 ml of a N,N-dimethylformamide solution containing 1.6 g (12.1 mmol) of (2S)-2-hydroxy-4-methylpentanoic acid synthesized in accordance with the method described in Tetrahedron, Vol 32, 1101 to 1106, 1976, and 18.64 g (109 mmol) of benzyl bromide, 13.9 g (60 mmol) of silver (I) oxide was added over a period of 40 minutes with stirring. The above prepared reaction mixture was further stirred at room temperature for 4 days and then diluted with ether, and insoluble materials were removed therefrom by filtration through Celite. The filtrate was washed successively with 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride. An organic layer and a water layer in the thus washed filtrate were separated. The resulting water layer was extracted with ethyl acetate again to obtain an another organic layer. The thus extracted layer and the first obtained organic layer were dried over anhydrous sodium sulfate and distilled away under reduced pressure. 1.44 g (36 mmol) of a sodium hydroxide aqueous solution was added to 200 ml of a methanol solution containing the residue thus obtained. The reaction mixture was stirred for 18 hours and concentrated under reduced pressure. The residue was dissolved in water and washed with ether twice. The resulting water layer was made acid (pH=1) with the addition of concentrated hydrochloric acid thereto and extracted with ethyl acetate twice. A mixture of the thus extracted layer and the originally obtained organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 2.15 g of the captioned Reference Compound No. 2-1 was obtained in a yield of 80%.

NMR (δ, $CDCl_3$) 7.26 - 7.40 (m, 5H), 4.74 (d, J=11Hz, 1H), 4.44 (d, J=11Hz, 1H), 3.99 - 4.04 (m, 1H), 1.73 - 1.95 (m, 2H), 1.50 - 1.70 (m, 1H), 0.93 (d, J=6Hz, 3H), 0.84 (d, J=6Hz, 3H)

Reference Example 2-2

Synthesis of (2S)-2-(3-phenylpropyloxy)-4-methylpentanoic acid (Reference Compound No. 2-2):



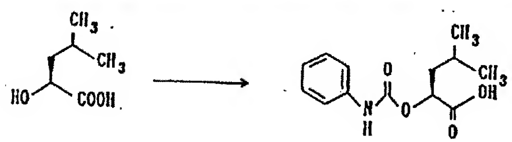
0.756 g (18.9 mmol) of sodium hydride (60% in oil) was added to 60 ml of a N,N-dimethyl-formamide suspension containing sodium chloride prepared by use of 2.5 g (18.9 mmol) of (2S)-2-hydroxy-4-

methylpentanoic acid and the above reaction mixture was stirred at 90°C for 7 hours. 11.28 g (56.7 mmol) of 3-phenylbromopropane and 0.641 g (1.89 mmol) of tetra-n-butylammonium hydrogensulfate were added to the reaction mixture, followed by stirring at 90°C for 18 hours. The temperature of the reaction mixture was decreased to room temperature. The reaction mixture was added to an iced water and extracted with ether twice. The resultant organic extract layer was washed successively with 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. 2.26 g (56.7 mmol) of a sodium hydroxide solution was added to 200 ml of a methanol solution containing the residue thus obtained. The above prepared reaction mixture was stirred for 18 hours and concentrated under reduced pressure. The residue thus obtained was dissolved in water and washed with ether twice. The resulting water layer was made acid (pH = 1) by the addition of concentrated hydrochloric acid and extracted with ethyl acetate twice. The resultant organic extract layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 1.078 g of the captioned Reference Compound No. 2-2 was obtained in a yield of 22%.

NMR (δ, $CDCl_3$) 7.15 - 7.31 (m, 5H), 3.85 - 3.95 (m, 1H), 3.59 - 3.70 (m, 1H), 3.35 - 3.45 (m, 1H), 2.65 - 2.80 (m, 2H), 1.80 - 2.00 (m, 1H), 1.50 - 1.80 (m, 2H), 0.85 - 1.00 (m, 6H)

Reference Example 2-3

Synthesis of (2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid (Reference Compound No. 2-3):



21.7 ml (0.2 mol) of isocyanic acid phenyl ester was added dropwise to a chloroform solution containing 13.3 g (0.1 mol) of (2S)-2-hydroxy-4-methylpentanoic acid and 20.3 ml (0.2 mol) of triethylamine under an ice-cooled condition with stirring. The above prepared reaction mixture was further stirred overnight and extracted with a 10% potassium carbonate solution. The resulting water layer was washed with chloroform. The water layer was made acid by the addition of concentrated hydrochloric acid, extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 10.5 g of the captioned Reference Compound No. 2-3 was obtained in a yield of 42%.

NMR (δ, $CDCl_3$) 7.28 - 7.40 (m, 4H), 7.08 (t, J = 7Hz, 1H), 6.80 - 6.90 (m, 1H), 5.14 (m, 1H), 4.70 - 5.30 (m, 1H), 1.70 - 1.88 (m, 3H), 0.99 (d, J = 3Hz, 3H), 0.97 (d, J = 3Hz, 3H)

Reference Examples 2-4 to 2-16

The same procedure as in Reference Example 2-3 was repeated except that the phenyl isocyanate employed in Reference Example 2-3 was replaced by the isocyanic acid derivative as shown in Table 13, whereby Reference Compound No. 2-4 to 2-16 (carboxylic acid derivatives (II-a)) shown in Table 13 were obtained.

Table 12

$$R^4\text{-NH-}\overset{\overset{X}{\|}}{C}O\text{-}\overset{\overset{R^2}{|}}{C}H\text{-COOH} \quad (II\text{-a})$$

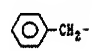
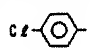
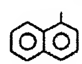
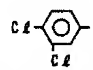
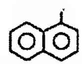
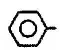
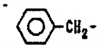
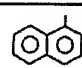
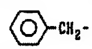
Ref. Ex.	Compound	R^4	R^2	X	NMR(δ, $CDCl_3$)
2-4	(2R)-2-(N-benzyl-carbamoyloxy)-4-methyl-pentanoic acid		$(CH_3)_2CH\text{-}CH_2\text{-}$	O	7.24 - 7.36 (m, 5H), 5.25 - 5.32 (m, 1H), 4.38 (d, J=6Hz, 2H), 4.24 - 4.30 (m, 1H), 1.58 - 1.81 (m, 3H), 0.93 - 0.98 (m, 6H)
2-5	(2S)-2-[N-(2-chloro-phenyl)carbamoyloxy]-4-methylpentanoic acid		$(CH_3)_2CH\text{-}CH_2\text{-}$	O	8.13 - 8.16 (m, 1H), 7.35 (dd, J=8Hz, J=2Hz, 1H), 7.28 (d, J=14Hz, 1H), 7.27(dd, J=16Hz, J=2Hz, 1H), 7.01 (dt, J=9Hz, J=2Hz, 1H), 5.12 - 5.17 (m, 1H), 1.72 - 1.91 (m, 3H), 0.97 (d, J=7Hz, 3H), 0.95 (d, J=4Hz, 3H)
2-6	(2S)-2-[N-(3-chloro-phenyl)carbamoyloxy]-4-methylpentanoic acid		$(CH_3)_2CH\text{-}CH_2\text{-}$	O	9.95 - 10.10 (brs, 1H), 7.49 (s, 1H), 7.19 (d, J=5Hz, 2H), 7.02 - 7.05 (m, 2H), 5.11 - 5.16 (m, 1H), 1.69 - 1.88 (m, 3H), 0.95 - 0.98 (m, 6H)
2-7	(2S)-2-[N-(4-chloro-phenyl)carbamoyloxy]-4-methylpentanoic acid		$(CH_3)_2CH\text{-}CH_2\text{-}$	O	9.50 - 9.80 (brs, 1H), 7.31 (d, J=9Hz, 2H), 7.24 (d, J=9Hz, 2H), 6.90 - 7.00 (m, 1H), 5.10 - 5.15 (m, 1H), 1.68 - 1.86 (m, 3H), 0.95 - 0.98 (m, 6H)
2-8	(2S)-2-[N-(1-naphthyl)-carbamoyloxy]-4-methyl-pentane acid		$(CH_3)_2CH\text{-}CH_2\text{-}$	O	7.81 - 7.92 (m, 4H), 7.68 (d, J=8Hz, 1H), 7.42 - 7.53 (m, 4H), 5.17 - 5.22 (m, 1H), 1.60 - 1.90 (m, 3H), 0.90 - 1.10 (m, 6H)
2-9	(2S)-2-(N-propylcarbamoyl-oxy)-4-methylpentanoic acid	$CH_3\text{-}(CH_2)_2\text{-}$	$(CH_3)_2CH\text{-}CH_2\text{-}$	O	5.60 - 5.90 (brs, 1H), 5.00 - 5.00 (m, 1H), 4.88 - 4.96 (m, 1H), 3.16 (q, J=65Hz, 2H), 1.54 - 1.82 (m, 8H), 0.94 - 0.98 (m, 6H)

Table 12

Ref. Ex.	Compound	R^4	R^2	X	NMR(δ,$CDCl_3$)
2-10	(2R)-2-[N-(t-butyl)-carbamoyloxy)-4-methyl-pentane acid	$(CH_3)C-$	$(CH_3)_2CH-CH_2-$	0	6.40 - 7.00 (brs, 1H), 4.92 - 5.12 (m, 1H), 4.81 - 4.90 (m, 1H), 1.61 - 1.88 (m, 3H), 1.33 (s, 9H), 0.97 (d, J=4Hz, 3Hz), 0.94 (d, J=4Hz, 3H)
2-11	(2S)-2-[N-(3,4-dichloro-phenyl)carbamoyloxy]-4-methylpentane acid		$(CH_3)_2CH-CH_2-$		7.62 (brs, 1H), 7.35 (d, J=7Hz, 1H), 7.18 (dd, J=7Hz, J=2Hz, 1H), 6.85 - 6.98 (m, 1H), 5.11 - 5.15 (m, 1H), 1.70 - 1.87 (m, 3H), 0.96 - 1.00 (m, 6H)
2-12	(2S)-2-(N-phenylthio-carbamoyloxy)-3-methyl-pentane acid		$(CH_3)_2CH-CH_2-$	0	7.37 - 7.40 (m, 2H), 7.31 (t, J=7Hz, 2H), 7,08 (t, J=7Hz, 1H), 6.77 - 6.87 (m, 1H), 5.11 - 5.17 (m, 1H), 1.70 - 1.87 (m, 3H), 0.95 - 1.00 (m, 6H)
2-13	(2S)-2-(N-phenylcarbamoyl-oxy)-3-methylpentane-acid		$(CH_3)_2CH-$	0	9.00 - 9.50 (brs, 1H), 7.26 - 7.39 (m, 4H), 7.04 - 7.09 (m, 1H), 6.90 - 7.05 (m, 1H), 5.00 (d, J=4Hz, 1H), 2.27 - 2.34 (m, 1H), 1.06 (d, J=7Hz, 3H), 1.03 (d, J=7Hz, 3H)
2-14	(2S)-2-[N-(1-naphthyl)-carbamoyloxy]-3-methyl-pentane acid		$(CH_3)_2CH-$	0	8.00 - 8.50 (brs, 1H), 7.67 - 7.95 (m, 5H) 7.42 - 7.53 (m, 3H), 5.03 (d, J=3Hz, 1H), 2.25 - 2.40 (m, 1H), 1.00 - 1.20 (m, 1H)
2-15	(2S)-2-(N-propylcarbamoyl-oxy)-3-methylpentane acid			0	8.35 - 8.70 (m, 1H), 7.17 - 7.25 (m, 10H), 6.97 - 7.02 (m, 1H), 5.23 - 5.27 (m, 1H), 3.23 (dd, J=14Hz, J=4Hz, 1H), 3.10 (dd, J=14Hz, J=9Hz, 1H)
2-16	(2S)-2-[N-(1-naphthyl)-carbamoyloxy]-3-phenyl propane acid			0	7.70 - 7.88 (m, 2H), 7.41 - 7.52 (m, 2H), 7.45 - 7.25 (m, 9H), 4.51 (m, 1H), 3.20 (dd, J=14Hz, J=4Hz, 1H), 3.10 - 3.35 (m, 1H), 2.99 (dd, J=14Hz, J=7Hz, 1H)

Reference Example 2-17

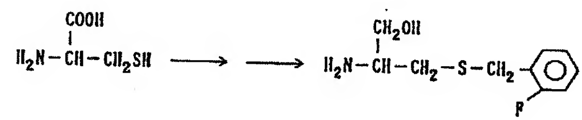
Synthesis of (2S)-2-amino-4-(methylthio)butanol (Reference Compound No. 2-17):

38 ml (300 mmol) of chlorotrimethylsilane was added to 200 ml of an anhydrous tetrahydrofuran suspension containing 3.3 g (150 mmol) of lithium boron hydride under an ice-cooled condition. The above prepared reaction mixture was stirred for 30 minutes and 7.5 g (50 mmol) of L-methionine was gradually added thereto, followed by stirring overnight at room temperature. Methanol was further added to the reaction mixture until the evolution of hydrogen gas ceased. The solvent was distilled away from the reaction mixture under reduced pressure. A 10% sodium hydroxide solution was added to the thus obtained residue, followed by the extraction with chloroform twice. The resultant extract layer was dried over anhydrous sodium sulfate and the solvent was distilled away under reduced pressure, whereby 5.12 g of the captioned Reference Compounds No. 2-17 was obtained in a yield of 75%.

NMR (δ, $CDCl_3$): 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.33 (dd, J=11Hz, J=7Hz, 1H), 2.98 - 3.04 (m, 1H), 2.57 - 2.64 (m, 2H), 2.22 - 2.43 (m, 3H), 2.11 (s, 3H), 1.68 - 1.80 (m, 1H), 1.50 - 1.62 (m, 1H)

Reference Example 2-18

Synthesis of (2R)-amino-3-(2-fluorobenzylthio)propanol (Reference Compound No. 2-18):



6.9 g (300 mmol) of metallic sodium was dissolved in 500 ml of methanol with stirring. 17.6 g (100 mmol) of a L-cysteine hydrochloride hydrate was added to the above prepared reaction mixture, followed by stirring at room temperature for one hour. 15.0 g (100 mmol) of 2-fluorobenzyl chloride was added dropwise to the reaction mixture, and the mixture was further stirred overnight. The solvent was distilled away from the reaction mixture under reduced pressure. The residue thus obtained was dissolved in water and washed with diethyl ether. The resulting water layer was made acid by the addition of concentrated hydrochloric acid, so that crystals separated out.

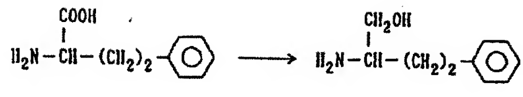
The crystals were separated from the reaction mixture by filtration, washed with water, ethanol and diethyl ether, and dried under reduced pressure, whereby 16.5 g of L-S-(2-fluorobenzyl)-cysteine was obtained in a yield of 72%.

The thus obtained L-S-(2-fluorobenzyl)-cysteine was reduced in accordance with the procedure used in Reference Example 2-17 subsequently, whereby the captioned Reference Compound No. 2-18 was obtained.

NMR (δ, $CDCl_3$) 7.20 - 7.38 (m, 2H), 7.01 - 7.13 (m, 2H), 3.75 (s, 2H), 3.62 (dd, J=11Hz, J=5Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 2.98 - 3.04 (m, 1H), 2.61 (dd, J=13Hz, J=5Hz, 1H), 2.42 (dd, J=13Hz, J=8Hz, 1H), 2.00 - 2.10 (m, 3H)

Reference Example 2-19

Synthesis of (2S)-2-amino-4-phenylbutanol (Reference Compound No. 2-19):

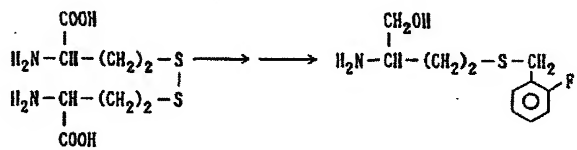


The same procedure as in Reference Example 2-17 was repeated except that the L-methionine was replaced by L-homophenylalanine, whereby the captioned Reference Compound No. 2-19 was obtained.

NMR (δ, $CDCl_3$) 7.17 - 7.31 (m, 5H), 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.31 (dd, J=11Hz, J=8Hz, 1H), 2.80 - 2.88 (m, 1H), 2.60 - 2.79 (m, 2H), 1.95 (br s, 3H), 1.70 - 1.80 (m, 1H), 1.52 - 1.64 (m, 1H)

Reference Example 2-20

Synthesis of (2S)-2-amino-4-(2-fluorobenzylthio)butanol (Reference Compound No. 2-20):



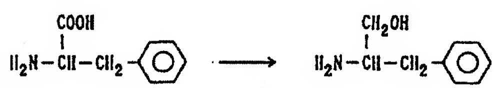
1.0 g of metallic sodium was added to liquid ammonia cooled at -78°, followed by stirring for 30 minutes. After the addition of 2.0 g (7.45 mmol) of homocystine, the above prepared reaction mixture was further stirred for 30 minutes. Ammonium chloride was added to the reaction mixture until the blue color of the reaction mixture faded and 2.17 g (15 mmol) of 2-fluorobenzyl chloride was further added thereto. The liquid ammonia was allowed to evaporate from the reaction mixture at room temperature. The residue thus obtained was dissolved in water, washed with diethyl ether, and made weakly acidic by the addition of concentrated hydrochloric acid, so that crystals were caused to separate out of the reaction mixture under a cooled condition. The crystals were separated by filtration and washed successively with water, ethanol and diethyl ether, and then dried under reduced pressure, whereby 1.80 g of (2S)-2-amino-4-(2-fluorobenzylthio)-butanoic acid was obtained in a yield of 81%.

The thus obtained (2S)-2-amino-4-(2-fluorobenzylthio)butanoic acid was reduced in accordance with the procedure used in Reference Example 2-17 subsequently, whereby the captioned Reference Compound No. 2-20 was obtained.

NMR (δ, $CDCl_3$) 7.13 - 7.36 (m, 2H), 7.01 - 7.13 (m, 2H), 3.75 (s, 2H), 3.55 (dd, J=11Hz, J=4Hz, 1H), 3.28 (dd, J=11Hz, J=8Hz, 1H), 2.88 - 2.97 (m, 1H), 2.48 - 2.62 (m, 2H), 1.95 - 2.10 (m, 3H), 1.65 - 1.77 (m, 1H), 1.47 - 1.59 (m, 1H)

Reference Example 2-21

Synthesis of (2S)-2-amino-3-phenylpropanol (Reference Compound No. 2-21):

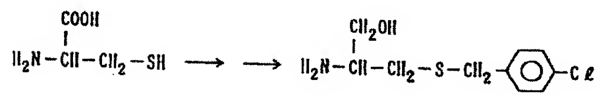


The same procedure as in Reference Example 2-17 was repeated except that the L-methionine was replaced by L-phenylalanine, whereby the captioned Reference Compound No. 2-21 was obtained.

NMR (δ, $CDCl_3$) 7.16 - 7.33 (m, 5H), 3.64 (dd, J=11Hz, J=4Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 3.07 - 3.16 (m, 1H), 2.79 (dd, J=14Hz, J=5Hz, 1H), 2.52 (dd, J=14Hz, J=9Hz, 1H), 2.10 (br s, 3H)

Reference Example 2-22

Synthesis of (2R)-2-amino-3-[(4-chlorobenzyl)thio]propanol (Reference Compound No. 2-22):

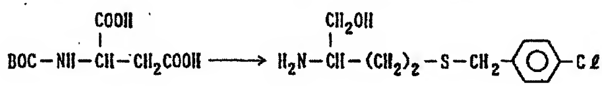


The same procedure as in Reference Example 2-18 was repeated except that the ortho-fluorobenzyl chloride was replaced by para-chlorobenzyl chloride, whereby the captioned Reference Compound No. 2-22 was obtained.

NMR (δ, $CDCl_3$) 7.23 - 7.30 (m, 5H), 3.68 (s, 2H), 3.60 (dd, J=11Hz, J=4Hz, 1H), 3.38 (dd, J=11Hz, J=7Hz, 1H), 2.92 - 3.00 (m, 1H), 2.54 (dd, J=13Hz, J=5Hz, 1H), 2.36 (dd, J=13Hz, J=8Hz, 1H), 2.16 - 2.28 (m, 3H)

Reference Example 2-23

Synthesis of (2S)-2-amino-4-[(4-chlorobenzyl)thio]butanol (Reference Compound No. 2-23):



40.1 g (0.4 mol) of potassium carbonate was added to an anhydrous dimethylformamide solution containing 23.4 g (0.1 mol) of t-butoxycarbonyl-L-aspartic acid. The above prepared mixture was stirred at room temperature for 2 hours, and then 31.1 ml (0.5 mol) of methyl iodide was added dropwise thereto. The reaction mixture was further stirred overnight and water was then added thereto, followed by the extraction with ethyl acetate. The resultant organic extract layer was washed with 1 N hydrochloric acid, a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, whereby 25.8 g of L-t-butoxycarbonylaspartic acid dimethyl ester was obtained in a yield of 99%.

25.7 g (98.4 mmol) of the above prepared diester was added to a tetrahydrofuran suspension containing 4.3 g (196.8 mmol) of lithium boron hydride. To this reaction mixture, 50 ml of methanol was further added dropwise with stirring under an ice-cooled condition, followed by stirring for 2 hours. Water was added to the reaction mixture and the solvent was distilled away therefrom under reduced pressure. The residue thus obtained was made acid by the addition of 1 N hydrochloric acid, extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 18.5 g of a diol was obtained in a yield of 92%.

83 ml (675 mmol) of 2,2-dimethoxypropane and 1.28 g (6.75 mmol) of paratoluene sulfonic acid were added to a methylene chloride solution containing 27.6 g (153 mmol) of the above prepared diol. The reaction mixture was stirred overnight at room temperature, washed with a saturated aqueous solution of sodium hydrogencarbonate, and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure. The thus obtained residue was chromatographed on a silica gel column for purification, whereby 19.9 g of (4S)-N-t-butoxycarbonyl-2,2-dimethyl-4-(2-hydroxyethyl)-1,3-

oxazolidine in a yield of 60%.

NMR (δ, $CDCl_3$): 4.18 - 4.27 (m, 1H), 3.99 - 4.04 (m, 1H), 3.50 - 3.71 (m, 3H), 2.70 - 3.00 (br s, 1H), 1.70 - 1.90 (m, 2H), 1.55 (s, 6H), 1.50 (s, 9H)

2.77 g (27.4 mmol) of triethylamine was added to an ethyl acetate solution containing 5.6 g (22.8 mmol) of the above prepared (4S)-N-t-butoxycarbonyl-2,2-dimethyl-4-(2-hydroxyethyl)-1,3-oxazolidine. Under an ice-cooled condition, 2.2 ml (27.4 mmol) of methanesulfonyl chloride was further added dropwise to the above reaction mixture, followed by stirring for 2 hours. The reaction mixture was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure, whereby 7.38 g of a methanesulfonate was obtained in a yield of 100%.

1.05 g (26.2 mmol) of sodium hydride (60% in oil) was added to an anhydrous N,N-dimethylformamide solution containing 3.72 ml (28.6 mmol) of 4-chlorobenzylmercaptan, followed by stirring at room temperature for 30 minutes. With the addition of 7.7 g (23.8 mmol) of the above prepared methanesulfonate, the reaction mixture was further stirred overnight. With the addition of water, the reaction mixture was extracted with ethyl acetate. The resultant organic extract layer was washed successively with 1 N hydrochloric acid and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure and the residue thus obtained was chromatographed on a silica gel column for purification, whereby 3.96 g of (4S)-N-t-butoxycarbonyl-2,2-dimethyl-4-[2-(4-chlorobenzylthio)]ethyl-1,3-oxazolidine was obtained in a yield of 43%.

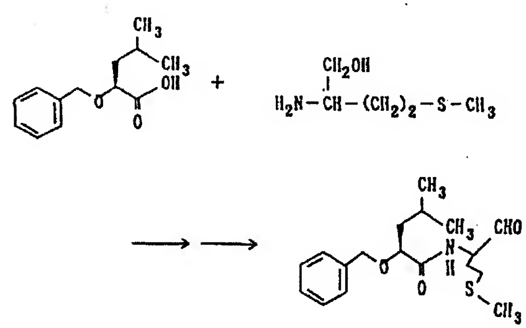
NMR (δ, $CDCl_3$) 7.28 (d, J=10Hz, 2H), 7.24 (d, J=10Hz, 2H), 3.94 - 4.02 (m, 1H), 3.85 - 3.92 (m, 1H), 3.68 (s, 2H), 3.66 - 3.70 (m, 1H), 2.32 - 2.42 (m, 2H), 1.70 - 2.08 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H)

8 ml of ethyl acetate containing 4 N hydrogen chloride (4 N HCl - AcOEt) was added to a methanol solution containing 1.70 g (4.4 mmol) of the above prepared (4S)-N-t-butoxycarbonyl-2,2-dimethyl-4-[2-(4-chlorobenzylthio]ethyl-1,3-oxazolidine. This reaction mixture was stirred overnight under an ice-cooled condition, and the solvent was distilled away therefrom under reduced pressure. The residue thus obtained was dissolved in water and washed with diethyl ether. The resulting water layer was made basic by the addition of a 10% potassium carbonate solution and extracted with chloroform. The extract layer was dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, whereby 0.81 g of the captioned Reference Compound No. 2-23 was obtained in a yield of 75%.

NMR (δ, $CDCl_3$): 7.23 - 7.30 (m, 4H), 3.68 (s, 2H), 3.54 (dd, J=11Hz, J=4Hz, 1H), 3.27 (dd, J=11Hz, J=7Hz, 1H), 2.88 - 2.98 (m, 1H), 2.39 - 2.58 (m, 2H), 1.77 (br s, 3H), 1.64 - 1.74 (m, 1H), 1.45 - 1.55 (m, 1H)

Example 2-1

Synthesis of (2S)-2-benzyloxy-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide (Compound No. 2-1):



A methylene chloride solution containing 0.752 g (3.38 mmol) of (2S)-2-benzyloxy-4-methylpentanoic acid and 0.267 g (3.38 mmol) of pyridine synthesized in Reference Example 2-1 was cooled in an ice bath containing sodium chloride. 407 mg (3.38 mmol) of pivalic acid chloride was added dropwise to the above prepared solution with stirring. 20 minutes later, a methylene chloride solution containing 0.457 g (3.38 mmol) of (2S)-2-amino-4-(methylthio)butanol and 0.342 g (3.38 mmol) of triethylamine was further added dropwise to the reaction mixture. The temperature of the reaction mixture was raised to room temperature. The reaction mixture was stirred for 18 hours, washed with 1 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure. The residue thus obtained and 1.38 g (13.52 mmol) of triethylamine were dissolved in a solvent containing dimethylsulfoxide and methylene chloride at a mixing ratio of 1:1, and cooled in an ice bath containing sodium chloride.

An anhydrous dimethylsulfoxide solution containing 2.15 g (13.52 mmol) of pyridine•sulfur trioxide complex was added dropwise to the cooled reaction mixture. 30 minutes later, the reaction mixture was added to an iced water and extracted with ethyl acetate four times. The resultant organic extract layer was washed successively with a 10% citric acid aqueous solution, water, a saturated aqueous solution of sodium hydrogencarbonate, a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.535 g of the captioned Compound No. 2-1 was obtained in a yield of 50%.

Melting Point (°C)	82.4 to 84.1
NMR (δ, $CDCl_3$)	9.62 (s, 1H), 7.30 - 7.45 (m, 5H), 7.22 (d, J=7.8Hz, 1H), 4.60 - 4.70 (m, 2H), 4.50 (d, J=12Hz, 1H), 3.91 - 3.95 (m, 1H), 2.45 - 2.60 (m, 2H), 2.20 - 2.35 (m, 1H), 2.07 (s, 3H), 1.80 - 2.00 (m, 1H), 1.50 - 1.70 (m, 3H), 0.93 (d, J=6Hz, 3H), 0.87 (d, J=6Hz, 3H)
R_f values	0.28 (Developing Solvent A: mixture of hexane and ethyl acetate at a mixing ratio of 1:1) 0.35 (Developing Solvent B: mixture of methylene chloride and acetone at a mixing ratio of 10:1)

Examples 2-2 to 2-29

The same procedure as in Example 2-1 was repeated except that the (2S)-2-benzyloxy-4-methylpentanoic acid and the (2S)-2-amino-4-(methylthio)butanol used in Example 2-1 were respectively replaced by a carboxylic acid derivative (Material 1) and an amine derivative (Material 2) shown in Table 13, whereby Compound No. 2-2 to 2-29 (oxy acid derivatives) as given in Table 14 were obtained.

Furthermore, Table 15 shows the yield, the melting point or state, the NMR analysis data and the R_f values obtained by TLC analysis of each of the prepared oxy acid derivatives. The developing solvent A used in the TLC analysis is a mixture of hexane and ethyl acetate at a mixing ratio of 1:1, and the developing solvent B is a mixture of methylene chloride and acetone at a mixing ratio of 10:1.

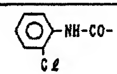
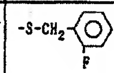
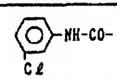
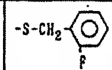
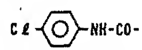
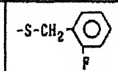
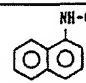
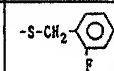
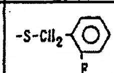
Table 13

$$R_3-O-\underset{\displaystyle |}{\overset{\displaystyle R^2}{CH}}-CH_2-CONH-\overset{\displaystyle CHO}{\overset{|}{CH}}-(CH_2)_n-R^1$$

Ex.	Material a (*)	Material b (*)	R_3	R_2	n	R_1	Compound
2-2	2-2	2-17	$C_6H_5-(CH_2)_3-$	$(CH_3)_2CH-CH_2-$	2	$-S-CH_3$	(2S)-2-(3-phenylpropyloxy-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-3	2-3	2-17	$C_6H_5-NH-CO-$	$(CH_3)_2CH-CH_2-$	2	$-S-CH_3$	(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-4	2-4	2-17	$C_6H_5-CH_2-NH-CO-$	$(CH_3)_2CH-CH_2-$	2	$-S-CH_3$	(2S)-2-(N-benzylcarbamoyloxy)-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-5	2-4	2-18	$C_6H_5-CH_2-NH-CO-$	$(CH_3)_2CH-CH_2-$	1	$-S-CH_2-C_6H_4F$ (2-F)	(2S)-2-(N-benzylcarbamoyloxy-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-6	2-3	2-18	$C_6H_5-NH-CO-$	$(CH_3)_2CH-CH_2-$	1	$-S-CH_2-C_6H_4F$ (2-F)	(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide

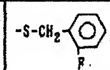
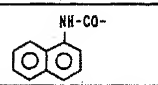
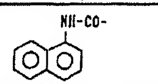
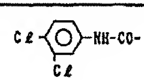
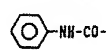
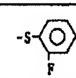
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 13

Ex.	Material a (*)	Material a (*)	R_3	R_2	n	R_1	Compound
2-7	2-5	2-18		$(CH_3)_2CH-CH_2-$	1		(2S)-2-[N-(2-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-8	2-6	2-18		$(CH_3)_2CH-CH_2-$	1		(2S)-2-[N-(3-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-9	2-7	2-18		$(CH_3)_2CH-CH_2-$	1		(2S)-2-[N-(4-chlorophenyl)carbamoyloxy]-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-10	2-8	2-18		$(CH_3)_2CH-CH_2-$	1		(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-11	2-9	2-18	$CH_3-(CH_2)_2-NH-CO-$	$(CH_3)_2CH-CH_2-$	1		(2S)-2-[N-propylcarbamoyloxy]-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide

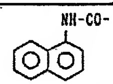
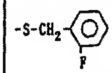
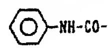
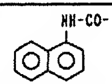
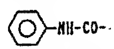
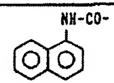
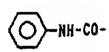
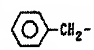
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 13

Ex.	Material a (*)	Material a (*)	R_3	R_2	n	R_1	Compound
2-12	2-10	2-18	$(CH_3)_3C$-NH-CO-	$(CH_3)_2CH-CH_2$-	1		(2S)-2-(N-t-butylcarbamoyloxy)-4-methylpentanoic acid-(1R)-[1-formyl-2-(2-fluorobenzylthio)]ethylamide
2-13	2-8	2-19		$(CH_3)_2CH-CH_2$-	2		(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid-(1S)-(1-formyl-3-phenyl)propylamide
2-14	2-8	2-17		$(CH_3)_2CH-CH_2$-	2	$-S-CH_3$	(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-15	2-11	2-17		$(CH_3)_2CH-CH_2$-	2	$-S-CH_3$	(2S)-2-[N-(3,4-dichlorophenyl)-carbamoyloxy]-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-16	2-12	2-17		$(CH_3)_2CH-CH_2$-	2	$-S-CH_3$	(2S)-2-(N-phenylthiocarbamoyloxy)-4-methylpentanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-17	2-3	2-20		$(CH_3)_2CH-CH_2$-	2		(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1S)-[1-formyl-3-(2-fluorobenzyl)thio)]propylamide

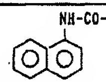
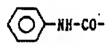
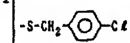
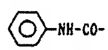
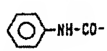
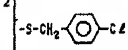
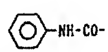
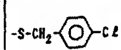
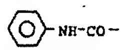
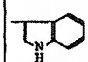
(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 13

Ex.	Material a (*)	Material a (*)	R_3	R_2	n	R_1	Compound
2-18	2-8	2-20		CH_3 $CH-CH_2-$ CH_3	2		(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid-(1S)-[1-formyl-3-(2-fluorobenzylthio)]propylamide
2-19	2-3	2-21		CH_3 $CH-CH_2-$ CH_3	1		(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1S)-(1-formyl-2-phenyl)ethylamide
2-20	2-8	2-21		CH_3 $CH-CH_2-$ CH_3	1		(2S)-2-[N-(1-naphthyl)carbamoyloxy]-4-methylpentanoic acid-(1S)-(1-formyl-2-phenyl)ethylamide
2-21	2-13	2-17		CH_3 $CH-$ CH_3	2	$-S-CH_3$	(2S)-2-(N-phenylcarbamoyloxy)-3-methylbutanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-22	2-14	2-17		CH_3 $CH-$ CH_3	2	$-S-CH_3$	(2S)-2-[N-(1-naphthyl)carbamoyloxy]-3-methylbutanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-23	2-15	2-17			2	$-S-CH_3$	(2S)-2-(N-phenylcarbamoyloxy)-3-phenylpropanoic acid-(1S)-(1-formyl-3-methylthio)propylamide

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 13

Ex.	Material a (*)	Material a (*)	R_3	R_2	n	R_1	Compound
2-24	2-16	2-17		CH_3, CH_3 >CH-CH_2-	2	-S-CH_3	(2S)-2-[N-(1-naphthyl)phenylcarbamoyloxy]-3-phenylpropanoic acid-(1S)-(1-formyl-3-methylthio)propylamide
2-25	2-13	2-22		CH_3, CH_3 >CH-	1		(2S)-2-(N-phenylcarbamoyloxy)-3-methylpentanoic acid-(1R)-(1-formyl-2-(4-chlorobenzylthio)]ethylamide
2-26	2-13	2-21		CH_3, CH_3 >CH-	1		(2S)-2-(N-phenylcarbamoyloxy)-3-methylbutanoic acid-(1S)-(1-(formyl-2-phenyl)ethylamide
2-27	2-3	2-23		CH_3, CH_3 >CH-CH_2-	2		(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1S)-[1-formyl-3-(4-chlorobenzylthio)]propylamide
2-28	2-13	2-23		CH_3, CH_3 >CH-	2		(2S)-2-(N-phenylcarbamoyloxy)-3-methylbutanoic acid-(1S)-[1-formyl-3-(4-chlorobenzylthio)]propylamide
2-29	2-3	1-52		CH_3, CH_3 >CH-CH_2-	1		(2S)-2-(N-phenylcarbamoyloxy)-4-methylpentanoic acid-(1S)-[1-formyl-2-(3-indolyl)]ethylamide

(*) Each material is indicated by the Reference Example Number in which it is synthesized.

Table 14

Ex.	Yield (%)	Melting Point (°C) or State	NMR(δ, $CDCl_3$)	R_f Values
2-2	49	amorphous	9.63 (s, 1H), 7.15 - 7.35 (m, 6H), 4.61 - 4.68 (m, 1H) 3.75 - 3.80 (m, 1H), 3.60 - 3.66 (m, 1H), 3.45 - 3.51 (m, 1H), 2.70 - 2.80 (m, 2H), 2.45 - 2.60 (m, 2H), 2.20 - 2.40 (m, 1H), 2.08 (s, 3H), 1.80 - 2.10 (m, 3H) 1.50 - 1.70 (m, 2H), 0.95 (d, J=6Hz, 3H), 0.94 (d, J=6Hz, 3H)	A:0.27 B:0.43
2-3	50	oily	9.62 (s, 1H), 7.30 - 7.45 (m, 4H), 7.10 (t, J=7.5Hz, 1H), 6.85 - 7.05 (m, 2H), 5.23 (t, J=7Hz, 1H), 4.57 (q, J=6Hz, 1H), 2.45 - 2.65 (m, 2H), 2.25 - 2.40 (m, 1H), 1.90 - 2.10 (m, 4H), 1.70 - 1.90 (m, 3H), 0.98 (d, J=6Hz, 6H)	A:0.21 B:0.32
2-4	45	oily	9.61 (s, 1H), 7.25 - 7.42 (m, 5H), 6.90 - 6.95 (m, 1H) 5.26 - 5.38 (m, 1H), 5.14 - 5.22 (m, 1H), 4.52 - 4.64 (m, 1H), 4.39 (d, J=4.5Hz, 2H), 2.40 - 2.60 (m, 2H), (m, 2H), 2.25 - 2.40 (m, 1H), 1.90 - 2.10 (m, 4H), 1.65 - 1.85 (m, 3H), 0.95 (d, J=5.4Hz, 6H)	A:0.16 B:0.26
2-5	35	95.6 - 97.2	9.55 (s, 1H), 7.23 - 7.34 (m, 7H), 7.00 - 7.13 (m, 2H) 6.98 (d, J=6Hz, 1H), 5.19 - 5.25 (m, 2H), 4.62 (q, J=6Hz, 1H), 4.38 - 4.41 (m, 2H), 3.75 (d, J=9Hz, 2H), 2.96 (q, J=6Hz, 2H), 1.58 - 1.78 (m, 3H), 0.94 - 0.97 (m, 6H)	A:0.17 B:0.30
2-6	51	oily	9.55 (s, 1H), 7.20 - 7.42 (m, 7H), 6.98 - 7.11 (m, 3H) 6.90 - 6.95 (m, 1H), 5.24 - 5.30 (m, 1H), 4.63 (dt, J=4Hz, 1H), 3.73 - 3.78 (m, 2H), 2.95 - 3.00 (m, 2H), 1.69 - 1.83 (m, 3H), 0.97 - 0.98 (m, 6H)	A:0.27 B:0.41
2-7	30	oily	9.56 (s, 1H), 8.12 (d, J=8Hz, 1H), 6.90 - 7.40 (m, 8H) 6.95 (d, J=6Hz, 1H), 5.20 - 5.30 (m, 1H), 4.60 - 4.70 (m, 1H), 3.75 (s, 2H), 2.90 - 3.05 (m, 2H), 1.70 - 1.90 (m, 3H), 0.98 (d, J=6Hz, 6H)	A:0.28 B:0.46
2-8	29	amorphous	9.55 (s, 1H), 7.52 (bs, 1H), 6.90 - 7.30 (m, 8H), 6.94 (bs, 1H), 5.25 (t, J=6Hz, 1H), 4.60 - 4.70 (m, 1H), 3.78 (s, 2H), 2.95 - 3.05 (m, 2H), 1.70 - 1.90 (m, 3H) 0.90 - 1.10 (m, 6H)	A:0.25 B:0.40
2-9	51	amorphous	9.56 (s, 1H), 6.90 - 7.40 (m, 10H), 5.26 (t, J=6Hz, 1H), 4.60 - 4.70 (m, 1H), 3.78 (s, 2H), 2.90 - 3.05 (m, 2H), 1.70 - 1.90 (m, 3H), 0.90 - 1.05 (m, 6H)	A:0.27 B:0.40

Table 14

Ex.	Yield (%)	Melting Point (°C) or State	NMR(δ, $CDCl_3$)	R_f Values
2-10	39	amorphous	9.54 (bs, 1H), 6.90 - 8.00 (m, 13H), 5.34 (t, J=6Hz, 1H), 4.55 - 4.70 (m, 1H), 3.71 (d, J=3Hz, 2H), 2.85 - 3.05 (m, 2H), 1.80 - 2.00 (m, 3H), 0.90 - 1.15 (m, 6H)	A:0.21 B:0.36
2-11	52	oily	9.57 (s, 1H), 6.90 - 7.40 (m, 5H), 5.19 (t, J=6Hz, 1H) 4.90 - 5.00 (m, 1H), 4.58 - 4.65 (m, 1H), 3.77 (d, J=3Hz, 2H), 3.10 - 3.25 (m, 2H), 2.97 (t, J=6Hz, 2H), 1.60 - 1.85 (m, 3H), 1.45 - 1.60 (m, 2H), 0.85 - 1.05 (m, 9H)	A:0.18 B:0.30
2-12	34	oily	9.55 (s, 1H), 7.00 - 7.40 (m, 4H), 6.95 (d, J=6Hz, 2H) 5.05 - 5.20 (m, 1H), 4.85 (bs, 1H), 4.61 (q, J=6Hz, 1H), 3.78 (d, J=6Hz, 2H), 2.90 - 3.05 (m, 2H), 2.60 - 2.80 (m, 3H), 1.33 (s, 9H), 0.94 (d, J=6Hz, 6H)	A:0.26 B:0.36
2-13	56	amorphous	9.52 (bs, 1H), 7.10 - 8.11 (m, 14H), 5.25 - 5.35 (m, 1H), 4.45 - 4.55 (m, 1H), 2.45 - 2.80 (m, 2H), 1.45 - 2.10 (m, 5H), 0.80 - 1.10 (m, 6H)	A:0.23 B:0.38
2-14	24	119.5 - 124.8	9.62 (s, 1H), 7.72 - 7.96 (m, 1H), 7.46 - 7.59 (m, 3H) 6.95 - 7.30 (m, 2H), 5.26 - 5.31 (m, 1H), 4.52 - 4.63 (m, 1H), 2.42 - 2.58 (m, 3H), 2.22 - 2.37 (m, 1H), 2.03 (s, 3H), 1.69 - 1.90 (m, 3H), 0.90 - 1.21 (m, 6H)	A:0.28 B:0.20
2-15	22	oily	9.65 (s, 1H), 7.62 - 7.64 (m, 1H), 7.37 (dd, J=9Hz, J=3Hz, 1H), 7.20 - 7.25 (m, 2H), 7.12 - 7.18 (m, 1H), 6.88 - 6.97 (m, 1H), 5.15 - 5.20 (m, 1H), 4.60 - 4.66 (m, 1H), 2.48 - 2.60 (m, 2H), 2.27 - 2.36 (m, 2H), 2.05 (s, 3H), 1.72 - 1.84 (m, 3H), 0.97 - 1.99 (m, 6H)	A:0.30 B:0.24
2-16	30	oily	9.63 (s, 1H), 7.30 - 7.42 (m, 4H), 7.10 (t, J=7Hz, 1H) 6.90 - 7.01 (m, 2H), 5.21 - 5.29 (m, 1H), 4.50 - 4.68 (m, 1H), 2.45 - 2.58 (m, 3H), 2.26 - 2.38 (m, 1H), 2.06 (s, 3H), 1.75 - 1.84 (m, 3H), 0.96 - 0.99 (m, 6H)	A:0.32 B:0.25
2-17	48	oily	9.56 (s, 1H), 7.12 - 7.41 (m, 6H), 7.00 - 7.12 (m, 3H) 6.83 - 6.92 (m, 2H), 5.20 - 5.28 (m, 1H), 4.52 - 4.64 (m, 1H), 3.71 (s, 2H), 2.47 - 2.55 (m, 2H), 2.20 - 2.37 (m, 1H), 1.92 - 2.04 (m, 1H), 1.71 - 1.81 (m, 3H) 0.95 - 0.98 (m, 6H)	A:0.37 B:0.32

Table 14

Ex.	Yield (%)	Melting Point (°C) or State	NMR(δ, $CDCl_3$)	R_f Values
2-18	8	99.8 - 104.0	9.56 (s, 1H), 7.86 - 7.94 (m, 3H), 7.70 - 7.73 (m, 1H) 7.45 - 7.58 (m, 3H), 7.03 - 7.24 (m, 3H), 6.98 - 7.08 (m, 2H), 5.26 - 5.31 (m, 1H), 4.50 - 4.61 (m, 1H), 3.64 - 3.68 (m, 2H), 2.38 - 2.55 (m, 1H), 2.20 - 2.31 (m, 1H), 1.68 - 1.98 (m, 5H), 0.90 - 1.00 (m, 6H)	A:0.31 B:0.21
2-19	60	117.5 - 122.1	9.64 (s, 1H), 7.21 - 7.39 (m, 7H), 7.08 - 7.15 (m, 3H) 6.67 - 6.77 (m, 1H), 6.61 - 6.71 (m, 1H), 5.22 (t, J=7Hz, 1H), 4.71 (q, J=7Hz, 1H), 3.21 (d, J=6Hz, 2H), 1.66 - 1.79 (m, 3H), 0.95 (d, J=6Hz, 6H)	A:0.31 B:0.21
2-20	9	123.4 - 129.2	9.62 (s, 1H), 7.71 - 7.91 (m, 4H), 7.45 - 7.57 (m, 3H) 7.00 - 7.30 (m, 6H), 6.60 - 6.80 (m, 1H), 5.27 (t, J=7Hz, 1H), 4.61 - 4.73 (m, 1H), 3.12 - 3.24 (m, 2H), 1.52 - 1.83 (m, 3H), 0.83 - 1.03 (m, 6H)	A:0.27 B:0.17
2-21	36	110.1 - 120.4	9.61 (s, 1H), 7.27 - 7.42 (m, 5H), 6.97 - 7.12 (m, 2H) 5.06 (d, J=5Hz, 1H), 4.56 (q, J=5Hz, 1H), 2.51 - 2.57 (m, 2H), 2.27 - 2.36 (m, 2H), 2.05 (s, 3H), 1.99 - 2.04 (m, 1H), 1.00 - 1.06 (m, 6H)	A:0.40 B:0.20
2-22	23	137.2 - 138.7	9.61 (s, 1H), 7.88 - 7.99 (m, 3H), 7.73 - 7.83 (m, 2H) 7.46 - 7.59 (m, 2H), 6.90 - 7.30 (m, 2H), 5.12 (d, J=5Hz, 1H), 4.50 - 4.70 (m, 1H), 2.26 - 2.55 (m, 4H), 2.03 (s, 3H), 1.90 - 2.00 (m, 1H), 0.90 - 1.10 (m, 6H)	A:0.36 B:0.15
2-23	32	112.5 - 116.2	9.51 (s, 1H), 7.10 - 7.37 (m, 10H), 6.92 - 7.03 (m, 1H), 6.72 - 6.88 (m, 1H), 5.44 - 5.48 (m, 1H), 4.48 - 4.54 (m, 1H), 2.17 - 2.40 (m, 3H), 1.98 (s, 3H), 1.87 - 1.95 (m, 1H)	A:0.41 B:0.32
2-24	7	127.0 - 116.2	9.51 (s, 1H), 7.42 - 7.92 (m, 7H), 6.90 - 7.40 (m, 7H) 5.52 (t, J=5Hz, 1H), 4.40 - 4.60 (m, 1H), 3.42 - 3.49 (m, 2H), 2.00 - 2.45 (m, 3H), 1.95 (br s, 3H), 1.81 - 1.85 (m, 1H)	A:0.32 B:0.16
2-25	37	118.1 - 125.4	9.53 (s, 1H), 7.10 - 7.42 (m, 9H), 6.97 - 7.08 (m, 2H) 5.07 - 5.13 (m, 1H), 4.57 - 4.67 (m, 1H), 3.65 (s, 2H) 2.86 - 2.92 (m, 2H), 2.25 - 2.40 (m, 1H), 0.99 - 1.06 (m, 6H)	A:0.44 B:0.28

Table 14

Ex.	Yield (%)	Melting Point (°C) or State	NMR(δ, $CDCl_3$)	R_f Values
2-26	19	112.0 - 116.2	9.62 (s, 1H), 7.08 - 7.40 (m, 10H), 6.80 (br s, 1H), 6.62 - 6.64 (m, 1H), 5.05 (d, J=5Hz, 1H), 4.71 (q, J=7Hz, 1H), 3.13 - 3.23 (m, 2H), 1.60 - 1.75 (m, 1H), 0.98 (d, J=7Hz, 3H), 0.91 (q, J=7Hz, 3H)	A:0.36 B:0.23
2-27	26	oily	9.58 (s, 1H), 7.10 - 7.42 (m, 9H), 6.92 - 7.00 (m, 1H) 6.78 - 6.90 (m, 1H), 5.09 (d, J=4Hz, 1H), 4.63 (q, J=5Hz, 1H), 3.58 (s, 2H), 2.41 - 2.51 (m, 2H), 2.20 - 2.40 (m, 1H), 1.90 - 1.98 (m, 1H), 1.41 - 1.73 (m, 1H) 0.96 - 1.04 (m, 6H)	A:0.41 B:0.25
2-28	24	amorphous	9.56 (s, 1H), 7.08 - 7.40 (m, 9H), 6.80 - 6.91 (m, 2H) 5.17 - 5.28 (m, 1H), 4.52 - 4.65 (m, 1H), 3.63 (s, 2H) 2.38 - 2.52 (m, 2H), 2.20 - 2.41 (m, 1H), 1.88 - 1.99 (m, 1H), 1.55 - 1.85 (m, 3H), 0.96 - 0.99 (m, 6H)	A:0.44 B:0.34
2-29	40	amorphous	9.54 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.63 (d, J=8Hz, 1H), 7.50 (d, J=8Hz, 1H), 6.90 - 7.30 (m, 8H), 6.80 (d, J=7Hz, 1H), 5.20 - 5.30 (m, 1H), 4.65 - 4.75 (m, 1H), 3.40 (dd, J=15Hz, 5Hz, 1H), 1.60 - 1.80 (m, 3H), 0.93 (d, J=6Hz, 6H), 3.25 (dd, J=15Hz, 7Hz, 1H)	A:0.52 B:0.21

Reference Example 3-1

Synthesis of L-O-(benzyl)serine ethyl ester hydrochloride (Reference Compound No. 3-1):

1 ml of concentrated hydrochloric acid was added to an ethanol solution containing 25 g (8.5 mmol) of L-N-(t-butoxycarbonyl)-O-(benzyl)serine, and the reaction mixture was stirred at room temperature for 2 hours.

The solvent was distilled away from the reaction mixture under reduced pressure. With the addition of 1.3 ml (17 mmol) of thionyl chloride, an ethanol solution of the thus obtained residue was stirred overnight at room temperature. The solvent was distilled away under reduced pressure, whereby 2.01 g of the captioned Reference Compound No. 3-1 was obtained in a yield of 91.6%.

NMR (δ, CD_3OD): 7.30 - 7.36 (m, 5H), 4.59 (dd, J=31.74Hz, J=12.15Hz, 2H), 4.24 - 4.31 (m, 3H), 3.93 (dd, J=10.53Hz, J=4.29Hz, 1H), 3.82 (dd, J=10.65Hz, J=3.33Hz, 1H), 1.27 (t, J=7.17Hz, 3H)

Reference Example 3-2

Synthesis of L-S-(2-phenylethyl)cysteine methyl ester hydrochloride (Reference Compound No. 3-2):

4.85 g (29.28 mmol) of a cysteine hydrochloride hydrate was added to 200 ml of a methanol solution of 4.74 g of sodium methoxide under an ice-cooled condition, and the mixture was stirred at room temperature for one hour. A methanol solution containing 5.55 g (30 mmol) of 2-bromoethylbenzene was added dropwise to the above prepared reaction mixture, and the mixture was stirred for one hour under an ice-cooled condition. The solvent was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in water, and washed with diethyl ether. The resultant water layer was made neutral with concentrated hydrochloric acid, so that crystals were caused to separat out.

The crystals separated by filtration were washed successively with water, ethanol and diethyl ether, and then dried, whereby 5.37 g of L-S-phenylethyl cysteine was obtained in a yield of 85.9%.

8.6 ml of thionyl chloride was added dropwise to 200 ml of a methanol solution containing 5.3 g (23.5 mmol) of the above obtained compound under an ice-cooled condition. After the completion of dropping, the reaction mixture was stirred overnight at room temperature. The solvent was distilled away under reduced pressure, so that crystals were caused to separated out. The thus obtained crystals were washed with

diethyl ether and dried, whereby 6.27 g of the captioned Reference Compound No. 3-2 was obtained in a yield of 96.3%.

NMR (δ, CD_3OD): 7.20 - 7.31 (m, 5H), 4.25 (dd, J=7.26Hz, J=4.23Hz, 1H), 3.83 (s, 3H), 3.12 (dd, J=14.49Hz, J=4.23Hz, 1H), 3.00 (dd, J=14.54Hz, J=7.27Hz, 1H), 2.82 - 2.94 (m, 4H)

Reference Example 3-3

Synthesis of L-S-(3-phenylpropyl)cysteine methyl ester hydrochloride (Reference Compound No. 3-3):

4.85 g (29.28 mmol) of a cysteine hydrochloride hydrate was added to 200 ml of a methanol solution of 4.75 g (87.84 mmol) of sodium methoxide under an ice-cooled condition, and the mixture was stirred at room temperature for one hour. A methanol solution containing 5.97 g (30 mmol) of 3-bromopropylbenzene was added dropwise to the above prepared reaction mixture, and the mixture was stirred for one hour under an ice-cooled condition. The solvent was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in water, and washed with diethyl ether. The resultant water layer became neutral with the addition of concentrated hydrochloric acid, so that crystals were caused to separate out.

The crystals separated by filtration were washed successively with water, ethanol and diethyl ether, and then dried, whereby 4.47 g of (L)-S-(3-phenylpropyl)cysteine was obtained in a yield of 63%.

6.7 ml of thionyl chloride was added dropwise to 200 ml of a methanol solution containing the above obtained compound under an ice-cooled condition. After the completion of dropping, the reaction mixture was stirred overnight at room temperature. The solvent was distilled away under reduced pressure, so that crystals were caused to separate out. The thus obtained crystals were washed with diethyl ether and dried, whereby 5.196 g of the captioned Reference Compound No. 3-3 was obtained.

NMR (δ, CD_3OD): 7.16 - 7.30 (m, 5H), 4.27 (dd, J=8.57Hz, J=4.18Hz, 1H), 3.82 (s, 3H), 3.15 (dd, J=14.54Hz, J=4.18Hz, 1H), 3.03 (dd, J=14.49Hz, J=7.54Hz, 1H), 2.73 (t, J=7.33Hz, 2H), 2.58 (t, J=7.54Hz, 2H), 1.86 - 1.97 (m, 2H)

Reference Example 3-4

Synthesis of L-O-(3-phenylpropyl)serine ethyl ester hydrochloride (Reference Compound No. 3-4):

1.28 g (32 mmol) of sodium hydride (60% in oil) was added to an anhydrous dimethylformamide solution containing 3.0 g (14.6 mmol) of L-N-(t-butoxycarbonyl)serine with stirring under an ice-cooled condition. After the temperature of the reaction mixture was raised to room temperature, the reaction mixture was stirred for 2 hours. After the addition of 3.18 g (16 mmol) of 3-bromopropylbenzene, the reaction mixture was further stirred overnight.

The reaction mixture was concentrated under reduced pressure. The residue thus obtained was dissolved in water and washed with diethyl ether. The resultant aqueous layer was made acid with the addition of a 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic extract layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure.

The residue thus obtained was dissolved in ethanol. With the addition of concentrated hydrochloric acid, the above prepared ethanol solution was stirred overnight. Then, 4 ml of thionyl chloride was added to the ethanol solution, the mixture was further stirred overnight. The solvent was distilled away from the reaction mixture under reduced pressure, so that crystals were obtained. The thus obtained crystals were washed with diethyl ether and dried, whereby 1.13 g of the captioned Reference Compound No. 3-4 was obtained.

NMR (δ, CD_3OD): 7.15 - 7.28 (m, 5H), 4.32 (q, J=6.52Hz, 2H), 4.25 (t, J=1.68Hz, 1H), 3.92 (dd, J=10.91Hz, J=4.40Hz, 1H), 3.82 (dd, J=10.04Hz, J=2.82Hz, 1H), 3.44 - 3.59 (m, 2H), 2.67 (t, J=7.32, 2H), 1.85 - 1.95 (m, 2H), 1.32 (t, J=7.49, 3H)

Reference Example 3-5

Synthesis of L-O-(thiophene-3-yimethyl)serine ethyl ester hydrochloride (Reference Compound No. 3-5):

172 g (43 mmol) of sodium hydride (60% in oil) was added to an anhydrous dimethylformamide solution containing 40 g (19.5 mmol) of (L)-N-(t-butoxycarbonyl)serine with stirring under an ice-cooled

condition. After the temperature of the reaction mixture was raised to room temperature, the reaction mixture was stirred for 2 hours. After the addition of 4.44 g (25 mmol) of 3-bromomethylthiophene, the reaction mixture was further stirred overnight.

The reaction mixture was concentrated under reduced pressure. The residue thus obtained was dissolved in water and washed with diethyl ether. The resultant water layer was made acid with the addition of a 1 N hydrochloric acid solution and extracted with ethyl acetate. The organic extract layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure.

The residue thus obtained was dissolved in ethanol. After the addition of 2.2 ml of concentrated hydrochloric acid, the above prepared ethanol solution was stirred overnight. Then, 2.3 ml of thionyl chloride was added to the ethanol solution, the mixture was further stirred overnight. The solvent was distilled away from the reaction mixture under reduced pressure, so that crystals were obtained. The thus obtained crystals were washed with diethyl ether and dried, whereby 1.25 g of the captioned Reference Compound No. 3-5 was obtained.

NMR (δ, CD_3OD): 7.38 - 7.42 (m, 2H), 7.08 - 7.10 (m, 1H), 4.60 (q, J=12.21Hz, 2H), 4.27 (q, J=7.11Hz, 1H), 4.21 (t, J=3.18Hz, 1H), 3.90 (dd, J=4.32Hz, J=9.87Hz, 1H), 3.81 (dd, J=3.27Hz, J=10.47Hz, 1H), 1.27 (t, J=7.11Hz, 3H)

Reference Example 3-6

Synthesis of L-S-(diphenylmethyl)cysteine methyl ester hydrochloride (Reference Compound No. 3-6):

3.0 g (17.1 mmol) of a L-cysteine hydrochloride hydrate and 3.15 g (17.1 mmol) of diphenylmethanol were added to 40 ml of trifluoroacetic acid, and the mixture was stirred at room temperature for one hour.

The trifluoroacetic acid was distilled away from the mixture under reduced pressure. The residue thus obtained was caused to crystallize with the addition of diethyl ether thereto, and washed successively with water, ethanol and diethyl ether, followed by drying under reduced pressure. Thus, 5.2 g of L-S-diphenylmethyl cysteine was obtained in a yield of 100%.

Under an ice-cooled condition, 1.0 ml of thionyl chloride was added dropwise to a methanol solution in which 1.0 g (3.5 mmol) of the above obtained L-S-diphenylmethyl cysteine was dissolved. After the completion of dropping, the temperature of the reaction mixture was raised to room temperature and the reaction mixture was stirred overnight. The solvent was distilled away from the reaction mixture under reduced pressure, so that crystals were obtained. The thus obtained crystals were washed with diethyl ether, whereby 1.11 g of the captioned Reference Compound No. 3-6 was obtained in a yield of 100%.

NMR (δ, $CDCl_3$): 7.41 - 7.44 (m, 4H), 7.15 - 7.29 (m, 6H), 5.42 (s, 1H), 4.22 - 4.32 (m, 1H), 3.61 (s, 3H), 2.98 - 3.03 (m, 2H), 2.78 - 2.89 (m, 2H)

Reference Example 3-7

Synthesis of L-S-(cyclohexylmethyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-7):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by cyclohexyl methyl bromide, so that the captioned Reference Compound No. 3-7 was obtained.

NMR (δ, $CDCl_3$): 4.35 - 4.39 (m, 1H), 4.30 (q, J=7.17Hz, 2H), 3.24 (d, J=5.22Hz, 2H), 2.50 (dd, J=6.90Hz, J=3.18, 2H), 2.20 - 2.65 (m, 2H), 1.38 - 1.88 (m, 5H), 1.33 (t, J=14.28, J=7.17, 3H), 0.87 - 1.28 (m, 6H)

Reference Example 3-8

Synthesis of L-S-(cyclopentyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-8):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by cyclopentyl bromide, so that the captioned Reference Compound No. 3-8 was obtained.

NMR (δ, CD_3OD): 4.44 (t, J=5.19Hz, 1H), 4.32 (t, J=6.99Hz, 2H), 4.27 - 4.29 (m, 1H), 3.31 - 3.46 (m, 4H), 3.17 (dd, J=17.19, J=4.77, 1H), 3.07 (dd, J=13.91, J=6.99, 1H), 2.00 - 2.11 (m, 1H), 1.72 - 1.81 (m, 1H), 1.48 - 1.68 (m, 2H), 1.35 (t, J=7.20Hz, 3H)

Reference Example 3-9

Synthesis of L-S-(thiophene-2-ylmethyl)cysteine methyl ester hydrochloride (Reference Compound No. 3-9):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by 2-chloromethylthiophene, so that the captioned Reference Compound No. 3-9 was obtained.

NMR (δ, CD_3OD): 7.34 (dd, J=5.26Hz, J=1.38Hz, 1H), 7.04 (d, J=4.56Hz, 1H), 6.95 (dd, J=5.04Hz, J=1.62Hz, 1H), 4.22 (dd, J=7.92Hz, J=4.5Hz, 1H), 4.06 (d, J=3.31Hz, 2H), 3.84 (s, 3H), 3.10 (dd, J=14.81Hz, J=4.56Hz, 1H), 2.96 (dd, J=14.92Hz, J=8.03Hz, 1H)

Reference Example 3-10

Synthesis of L-S-(thiophene-3-ylmethyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-10):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by 3-bromomethylthiophene, so that the captioned Reference Compound No. 3-10 was obtained.

NMR (δ, CD_3OD): 7.41 (dd, J=4.95Hz, J=2.01Hz, 1H), 7.32 (brs, 1H), 7.12 (d, J=4.89Hz, 1H), 4.29 (q, J=7.26Hz, 2H), 4.14 (dd, J=8.04Hz, J=3.57Hz, 1H), 3.87 (s, 2H), 3.03 (dd, J=14.76Hz, J=4.5Hz, 1H), 2.90 (dd, J=14.82Hz, J=8.13Hz, 1H), 1.31 (t, J=7.23Hz, 3H)

Reference Example 3-11

Synthesis of L-S-(1-naphthylmethyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-11):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by 1-naphthylmethyl bromide, so that the captioned Reference Compound No. 3-11 was obtained.

NMR (δ, CD_3OD): 8.18 (d, J=8.37Hz, 1H), 7.80 - 7.90 (m, 2H), 7.35 - 7.58 (m, 4H), 4.33 (s, 2H), 4.17 - 4.29 (m, 3H), 3.04 (dd, J=4.44Hz, J=9.72, 1H), 2.95 (dd, J=7.80Hz, J=14.64Hz, 1H), 1.25 (t, J=7.02Hz, 3H)

Reference Example 3-12

Synthesis of L-S-(2-naphthylmethyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-12):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by 2-naphthylmethyl bromide, so that the captioned Reference Compound No. 3-12 was obtained.

NMR (δ, CD_3OD): 7.81 - 7.88 (m, 4H), 7.47 - 7.55 (m, 3H), 4.21 - 4.25 (m, 2H), 4.13 - 4.20 (m, 1H), 4.00 (s, 2H), 3.01 (dd, J=9.78Hz, J=4.38Hz, 1H), 2.89 (dd, J=8.19Hz, J=6.39Hz, 1H), 1.22 (t, J=7.05Hz, 3H)

Reference Example 3-13

Synthesis of L-S-(2-chlorobenzyl)cysteine ethyl ester hydrochloride (Reference Compound No. 3-13):

The same reaction procedure as used in Reference Example 3-2 was repeated except that the 2-bromoethylbenzene used in Reference Example 3-2 was replaced by 2-chlorobenzyl chloride, so that the captioned Reference Compound No. 3-13 was obtained.

NMR (δ, CD_3OD): 7.41 - 7.48 (m, 2H), 7.28 - 7.31 (m, 2H), 4.30 (q, J=7.33Hz, 2H), 4.25 - 4.29 (m, 1H), 3.12 (dd, J=14.71Hz, J=4.45Hz, 1H), 2.97 (dd, J=14.65Hz, J=7.88Hz, 1H), 1.31 (t, J=7.16Hz, 3H)

Reference Example 3-14

Synthesis of (2R)-2-amino-3-(2-fluorobenzylthio)propanol (Reference Compound No. 3-14):

30.4 g (173 mmol) of a L-cysteine hydrochloride hydrate was added to a methanol solution containing sodium methoxide which was prepared using 12.0 g (519 mmol) of metallic sodium and 700 ml of methanol. To this mixture, 25.0 g (173 mmol) of 2-fluorobenzyl chloride was added dropwise, and the reaction mixture was stirred overnight at room temperature. The methanol was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in water and washed with ether twice. Then, the pH of the resultant water layer was adjusted to 7.0 with the addition of concentrated hydrochloric acid, so that crystals were caused to separate out.

These crystals were separated by filtration, washed successively with water, ethanol and diethyl ether, and dried under reduced pressure, whereby 29.7 g of (2R)-2-amino-3-(2-fluorobenzylthio)propionic acid was obtained in a yield of 74.8%.

6.7 ml (52.8 mmol) of chlorotrimethylsilane was added to an anhydrous tetrahydrofuran solution of 0.58 g (26.4 mmol) of lithium boron hydride, and the mixture was stirred at room temperature for 30 minutes. To this mixture, 2.02 g (8.8 mmol) of the above prepared (2R)-2-amino-3-(2-fluorobenzylthio)propionic acid was added, and the reaction mixture was further stirred overnight at room temperature. With the addition of methanol, the solvent was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in a 1 N sodium hydroxide solution and extracted with chloroform. After the extract layer was dried over anhydrous sodium sulfate, the solvent was distilled away under reduced pressure, whereby 1.69 g of the captioned Reference Compound No. 3-14 was obtained in a yield of 89.4%.

NMR (δ, $CDCl_3$): 7.19 - 7.38 (m, 2H), 7.00 - 7.12 (m, 2H), 3.75 (s, 2H), 3.65 (dd, J=10.86Hz, J=3.78Hz, 1H), 3.42 (dd, J=10.74Hz, J=6.45Hz, 1H), 3.00 - 3.10 (m, 1H), 2.80 (brs, 3H), 2.62 (dd, J=13.56Hz, J=4.92Hz, 1H), 2.45 (dd, J=13.35Hz, J=8.22Hz, 1H)

Reference Example 3-15

Synthesis of (2R)-2-amino-3-(3-chlorobenzylthio)propanol (Reference Compound No. 3-15):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 3-chlorobenzyl bromide, so that the captioned Reference Compound No. 3-15 was obtained.

NMR (δ, $CDCl_3$): 7.15 - 7.35 (m, 4H), 3.68 (s, 2H), 3.64 (d, J=3.52Hz, 1H), 3.44 (dd, J=6.45Hz, J=10.85Hz, 1H), 2.98 (brs, 4H), 2.60 (dd, J=5.21Hz, J=13.4Hz, 1H), 2.45 (dd, J=8.08Hz, J=13.45Hz, 1H)

Reference Example 3-16

Synthesis of (2R)-2-amino-3-(4-chlorobenzylthio)propanol (Reference Compound No. 3-16):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 4-chlorobenzyl chloride, so that the captioned Reference Compound No. 3-16 was obtained.

NMR (δ, $CDCl_3$): 7.26 (q, J=8.52, 4H), 3.68 (s, 2H), 3.60 (dd, J=4.02Hz, J=10.75Hz, 1H), 3.38 (dd, J=6.46Hz, J=10.8Hz, 1H), 2.96 (brs, 1H), 2.54 (dd, J=4.77Hz, J=13.18Hz, 1H), 2.36 (dd, J=8.25Hz, J=13.35Hz, 1H), 2.24 (brs, 3H)

Reference Example 3-17

Synthesis of (2R)-2-amino-3-(3-fluorobenzylthio)propanol (Reference Compound No. 3-17):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 3-fluorobenzyl chloride, so that the captioned Reference Compound No. 3-17 was obtained.

NMR (δ, $CDCl_3$): 7.21 - 7.28 (m, 1H), 6.89 - 7.10 (m, 3H), 4.76 (s, 3H), 3.76 (dd, J=3.42Hz, J=11.5Hz, 1H), 3.72 (s, 2H), 3.57 (dd, J=7.82Hz, J=12.59Hz, 1H), 3.25 (brs, 1H),

2.62 (d, J=7.05Hz, 2H)

Reference Example 3-18

Synthesis of (2R)-2-amino-3-(4-fluorobenzylthio)propanol (Reference Compound No. 3-18):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 4-fluorobenzyl chloride, so that the captioned Reference Compound No. 3-18 was obtained.

NMR (δ, $CDCl_3$): 7.25 - 7.30 (m, 2H), 6.97 - 7.03 (m, 2H), 3.69 (s, 2H), 3.60 (dd, J=4.23Hz, J=10.74Hz, 1H), 3.37 (dd, J=6.57Hz, J=10.74Hz, 1H), 2.95 (brs, 1H), 2.55 (dd, J=4.93Hz, J=13.29Hz, 1H), 2.01 (br d, J=10.25Hz, 3H), 2.36 (dd, J=8.31Hz, 13.30Hz, 1H)

Reference Example 3-19

Synthesis of (2R)-2-amino-3-(2-methoxybenzylthio)propanol (Reference Compound No. 3-19):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 2-methoxybenzyl chloride, so that the captioned Reference Compound No. 3-19 was obtained.

NMR (δ, $CDCl_3$): 7.21 - 7.26 (m, 2H), 6.86 - 6.94 (m, 2H), 3.85 (s, 3H), 3.74 (s, 2H), 3.62 (dd, J=10.74Hz, J=4.13Hz, 1H), 3.37 (dd, J=10.74Hz, J=6.73, 1H), 2.97 - 3.05 (m, 1H), 2.62 (dd, J=13.51Hz, J=4.83Hz, 1H), 2.40 (dd, J=13.57Hz, J=8.31Hz, 1H), 2.08 (brs, 3H)

Reference Example 3-20

Synthesis of (2R)-2-amino-3-(3-methoxybenzylthio)propanol (Reference Compound No. 3-20):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 3-methoxybenzyl chloride, so that the captioned Reference Compound No. 3-20 was obtained.

NMR (δ, $CDCl_3$): 7.22 (t, J=8.25, 1H), 6.88 (d, J=6.68Hz, 1H), 6.86 (s, 1H), 6.79 (dd, J=2.06Hz, J=7.48Hz, 1H), 3.80 (s, 3H), 3.68 (s, 2H), 3.58 (dd, J=4.18Hz, J=10.8Hz, 1H), 3.36 (dd, J=6.62Hz, J=10.75Hz, 1H), 2.90 - 3.00 (m, 1H), 2.56 (dd, J=4.68Hz, J=13.29Hz, 1H), 2.36 (dd, J=8.19Hz, J=13.35Hz, 1H), 2.11 (brs, 3H)

Reference Example 3-21

Synthesis of (2R)-2-amino-3-(4-methoxybenzylthio)propanol (Reference Compound No. 3-21):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 4-methoxybenzyl chloride, so that the captioned Reference Compound No. 3-21 was obtained.

NMR (δ, $CDCl_3$): 7.22 (d, J=8.63Hz, 2H), 6.85 (d, J=8.63Hz, 2H), 3.80 (s, 3H), 3.67 (s, 2H), 3.59 (dd, J=4.13Hz, J=10.74Hz, 1H), 3.36 (dd, J=6.62Hz, J=10.75Hz, 1H), 2.90 - 2.98 (m, 1H), 2.55 (dd; J=4.88Hz, J=13.29Hz, 1H), 2.36 (dd, J=8.24Hz, J=13.29Hz, 1H), 1.99 (s, 3H)

Reference Example 3-22

Synthesis of (2R)-2-amino-3-(3-nitrobenzylthio)propanol (Reference Compound No. 3-22):

The same reaction procedure as used in Reference Example 3-14 was repeated except that the 2-fluorobenzyl chloride used in Reference Example 3-14 was replaced by 3-nitrobenzyl chloride, so that the captioned Reference Compound No. 3-22 was obtained.

NMR (δ, $CDCl_3$): 8.20 (s, 1H), 8.13 (d, J=8.24Hz, 1H), 7.67 (d, J=7.75Hz, 1H), 7.51 (t, J=7.87Hz,

1H), 3.81 (s, 2H), 3.62 (dd, J=10.75Hz, J=4.24Hz, 1H), 3.42 (dd, J=10.75Hz, J=6.35Hz, 1H), 3.00 - 3.08 (m, 1H), 2.58 (dd, J=13.18Hz, J=4.94Hz, 1H), 2.41 (dd, J=13.23Hz, J=8.13Hz, 1H), 2.05 (brs, 3H)

Reference Example 3-23

Synthesis of (2R)-2-amino-3-(4-nitrobenzylthio)propanol (Reference Compound No. 3-23):

To a 1 N sodium hydroxide aqueous solution, 5.27 g (30 mmol) of a L-cysteine hydrochloride hydrate was added. Subsequently, a dioxane solution containing 5.15 g (30 mmol) of 4-nitrobenzyl chloride was added dropwise to the above mixture. The thus obtained reaction mixture was stirred at room temperature for one hour. The reaction mixture was washed with diethyl ether and made weakly acidic with the addition of concentrated hydrochloric acid. On cooling the reaction mixture, crystals were caused to separate out.

The crystals thus obtained were separated by filtration, washed successively with ethanol and diethyl ether, and then dried under reduced pressure, whereby 3.55 g of L-2-amino-3-(4-nitrobenzylthio)propionic acid was obtained in a yield of 45.9%.

9.5 ml (75 mmol) of chlorotrimethylsilane was added to an anhydrous tetrahydrofuran solution of 0.82 g (37.5 mmol) of lithium boron hydride, and the mixture was stirred at room temperature for 30 minutes. To this mixture, 3.0 g (11.70 mmol) of the above prepared L-2-amino-3-(4-nitrobenzylthio)propionic acid was added, and the reaction mixture was further stirred overnight at room temperature. With the addition of methanol, the solvent was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in a 1 N sodium hydroxide solution and extracted with chloroform. After the extract layer was dried over anhydrous sodium sulfate, the solvent was distilled away under reduced pressure, whereby 2.52 g of the captioned Reference Compound No. 3-23 was obtained in a yield of 89%.

NMR (δ, $CDCl_3$): 8.19 (d, J=8.63Hz, 2H), 7.50 (d, J=8.69Hz, 2H), 3.80 (s, 2H), 3.60 (dd, J=4.18Hz, J=10.74Hz, 1H), 3.40 (dd, J=6.35Hz, J=10.74Hz, 1H), 2.92 - 3.02 (m, 1H), 2.57 (dd, J=4.94Hz, J=13.19Hz, 1H), 2.39 (dd, J=8.13Hz, J=13.18Hz, 1H), 2.01 (s, 3H)

Reference Example 3-24

Synthesis of (2S)-2-amino-4-phenyloxybutanol hydrochloride (Reference Compound No. 3-24):

320 g (2.94 mol) of ethyl bromide was added dropwise to an anhydrous dimethylformamide solution containing 142 g (0.59 mol) of L-N-(t-butoxycarbonyl)-homoserine potassium salt synthesized in accordance with the method described in Tetrahedron Letters vol. 20, 2243, (1978). The thus obtained reaction mixture was stirred overnight at room temperature. The solvent was distilled away from the reaction mixture under reduced pressure.

The residue thus obtained was dissolved in water, and extracted with ethyl acetate. The extract layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The thus obtained residue was chromatographed on a silica gel column for purification, whereby 44.5 g of L-N-(t-butoxycarbonyl)homoserine ethyl ester was obtained in a yield of 31%.

3.44 g (30 mmol) of methanesulfonyl chloride was added to an ethyl acetate solution containing 6.18 g (25 mmol) of the above prepared L-N-(t-butoxycarbonyl)-homoserine ethyl ester and 3.04 g (30 mmol) of triethylamine with stirring under an ice-cooled condition. The thus obtained reaction mixture was stirred for one hour. The reaction mixture was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, so that 8.12 g of a methanesulfonate was obtained in a yield of 100%.

0.35 g of sodium hydride (60% in oil) was added to an anhydrous dimethylformamide solution containing 0.88 g of phenol, and the mixture was stirred for one hour. To this mixture, a dimethylformamide solution of 2.55 g (7.83 mmol) of the above prepared methanesulfonate was added dropwise, and the thus obtained reaction mixture was stirred overnight at room temperature. With the addition of a saturated aqueous solution of ammonium chloride, the reaction mixture was extracted with ethyl acetate. The extract layer was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and water, and then dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 2.13 g of L-N-

(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester was obtained in a yield of 84%.

NMR (δ, $CDCl_3$): 7.20 - 7.30 (m, 2H), 6.83 - 6.97 (m, 3H), 5.34 - 5.42 (m, 1H), 4.45 - 4.52 (m, 1H), 4.18 (q, J=7.22Hz, 2H), 4.04 (t, J=6.08Hz, 2H), 2.20 - 2.37 (m, 2H), 1.44 (s, 9H), 1.25 (t, J=7.06Hz, 3H)

0.28 g of lithium borohydride was added to a tetrahydrofuran solution containing 2.10 g (6.5 mmol) of the above prepared L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester, followed by dropping of methanol with stirring under an ice-cooled condition. After the reaction mixture was stirred for one hour, water was added to the reaction mixture and the solvent was distilled away therefrom under reduced pressure.

With the addition of a 1 N hydrochloric acid aqueous solution, the thus obtained residue was extracted with ethyl acetate. The resultant extract organic layer was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate, and then the solvent was distilled away under reduced pressure.

The residue thus obtained was dissolved in 4 N HCl - AcOEt, and the solution was stirred for one hour. The solvent was distilled away from the reaction solution under reduced pressure, whereby 0.64 g of the captioned Reference Compound No. 3-24 was obtained in a yield of 46%.

Reference Example 3-25

Synthesis of (2S)-2-amino-4-(phenylthio)butanol hydrochloride (Reference Compound No. 3-25):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and thiophenol, so that L-N-(t-butoxycarbonyl)-S-phenylhomocystein benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.16 - 7.37 (m, 10H), 5.15 (d, J=3.31Hz, 2H), 5.09 - 5.20 (m, 1H), 4.47 - 4.53 (m, 1H), 2.90 (dt, J=6.3Hz, J=2.11, 2H), 2.10 - 2.20 (m, 1H), 1.89 - 2.00 (m, 1H), 1.43 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-25 was obtained.

Reference Example 3-26

Synthesis of (2R)-2-amino-3-(2-chlorobenzyloxy)propanol hydrochloride (Reference Compound No. 3-26):

3.0 g of sodium hydride (60% in oil) was added to an anhydrous dimethylformamide solution containing 7.0 g (34 mmol) of L-N-(t-butoxycarbonyl)serine, and the mixture was stirred at room temperature for three hours. To this mixture, 6.0 g (37 mmol) of 2-chlorobenzyl chloride was added dropwise, and the thus obtained reaction mixture was stirred overnight at room temperature. The solvent was distilled away from the reaction mixture under reduced pressure.

The thus obtained residue was dissolved in a mixed solvent of ethyl acetate and 1 N hydrochloric acid. The resultant ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled away, whereby 4.3 g of L-N-(t-butoxycarbonyl)-O-(2-chlorobenzyl)-serine was obtained in a yield of 38%.

0.93 g of ethyl chlorocarbonate was added dropwise to a tetrahydrofuran solution containing 2.15 g (6.5 mmol) of the above prepared L-N-(t-butoxycarbonyl)-O-(2-chlorobenzyl)-serine and triethylamine by cooling in an ice bath containing salt. After this reaction mixture was stirred for 2 hours, crystals were caused to separate out.

These crystals were removed by filtration, and sodium boron hydride and methanol were successively added dropwise to the filtrate with stirring under an ice-cooled condition. The reaction mixture was stirred for 2 hours. The solvent was distilled away from the reaction mixture under reduced pressure.

With the addition of a 1 N hydrochloric acid aqueous solution, an aqueous solution of the above obtained residue was extracted with ethyl acetate. The resultant extract organic layer was washed successively with a 10% aqueous solution of sodium hydroxide and water and dried over anhydrous sodium sulfate, and then the solvent was distilled away. The residue thus obtained was chromatographed on a silica gel column for purification, so that 0.81 g of an alcohol was obtained.

The thus obtained alcohol was dissolved in 4 N HCl - AcOEt, and the solution was stirred at room temperature for 30 minutes. The solvent was distilled away from the reaction solution, whereby 0.55 g of the

captioned Reference Compound No. 3-26 was obtained in a yield of 19%.

NMR (δ, CD_3OD): 7.53 - 7.56 (m, 1H), 7.39 - 7.42 (m, 1H), 7.30 - 7.35 (m, 2H), 4.70 (s, 2H), 3.67 - 3.82 (m, 4H), 3.42 - 3.49 (m, 1H)

Reference Example 3-27

Synthesis of (2S)-2-amino-4-(2-fluorophenyloxy)butanol hydrochloride (Reference Compound No. 3-27):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the phenol used in Reference Example 3-24 was replaced by 2-fluorophenol, so that L-N-(t-butoxycarbonyl)-O-(2-fluorophenyl)homoserine ethyl ester was obtained.

NMR (δ, $CDCl_3$): 6.85 - 7.10 (m, 4H), 5.40 - 5.46 (m, 1H), 4.42 - 4.51 (m, 1H), 4.22 (q, J=7.0Hz, 2H), 4.12 (q, J=5.48Hz, 2H), 2.23 - 2.41 (m, 2H), 1.44 (s, 9H), 1.26 (t, J=7.16Hz, 3H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-27 was obtained.

Reference Example 3-28

Synthesis of (2S)-2-amino-4-(3-fluorophenyloxy)butanol hydrochloride (Reference Compound No. 3-28):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the phenol used in Reference Example 3-24 was replaced by 3-fluorophenol, so that L-N-(t-butoxycarbonyl)-O-(3-fluorophenyl)homoserine ethyl ester was obtained.

NMR (δ, $CDCl_3$): 7.11 - 7.24 (m, 1H), 6.55 - 6.69 (m, 3H), 5.31 - 5.38 (m, 1H), 4.45 - 4.51 (m, 1H), 4.20 (q, J=7.16Hz 2H), 4.03 (t, J=6.02Hz, 2H), 2.20 - 2.38 (m, 2H), 1.44 (s, 9H), 1.26 (t, J=7.11Hz, 3H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-28 was obtained.

Reference Example 3-29

Synthesis of (2S)-2-amino-4-(2-chlorophenyloxy)butanol hydrochloride (Reference Compound No. 3-29):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and 2-chlorophenol, so that L-N-(t-butoxycarbonyl)-O-(2-chlorophenyl)-homoserine benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.30 - 7.36 (m, 6H), 7.18 (dt, J=6.67Hz, J=1.6, 1H), 6.90 (dt, J=6.3Hz, J=1.35Hz, 1H), 6.80 (d, J=8.24Hz, 1H), 5.80 - 5.83 (m, 1H), 5.18 (d, J=2.17Hz, 2H), 4.55 - 4.62 (m, 1H), 4.07 - 4.14 (m, 1H), 3.95 - 4.00 (m, 1H), 2.40 - 2.50 (m, 2H), 1.43 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-29 was obtained.

Reference Example 3-30

Synthesis of (2S)-2-amino-4-(3-chlorophenyloxy)butanol hydrochloride (Reference Compound No. 3-30):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and 3-chlorophenol, so that L-N-(t-butoxycarbonyl)-O-(3-chlorophenyl)-homoserine benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.34 (s, 5H), 7.16 (t, J=8.14Hz, 1H), 6.92 (dd, J=5.53Hz, J=1.96Hz, 1H), 6.80 (s,

1H), 6.69 (dd, J=6.35Hz, J=2.01, 1H), 5.25 - 5.30 (m, 1H), 5.18 (d, J=2.23Hz, 2H), 4.50 - 4.57 (m, 1H), 3.98 (t, J=5.96Hz, 2H), 2.25 - 2.37 (m, 2H), 1.43 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-30 was obtained.

Reference Example 3-31

Synthesis of (2S)-2-amino-4-benzylthiobutanol (Reference Compound No. 3-31):

1 g of metallic sodium was added to liquid ammonia which was cooled to -78°C, and the mixture was stirred for 30 minutes. With the addition of 2.0 g (7.45 mmol) of homocysteine, the reaction mixture was further stirred for 30 minutes. Ammonium chloride was added to the above reaction mixture until a blue color of the mixture faded. Subsequently, with the addition of 0.69 g (30 mmol) of benzyl bromide, the liquid ammonia was allowed to evaporate at room temperature.

The thus obtained residue was dissolved in water and washed with diethyl ether, and the above prepared solution was made weakly acidic with the addition of concentrated hydrochloric acid, and crystals were allowed to separate out in the cool place.

The thus obtained crystals were washed successively with water, ethanol and ether, and dried under reduced pressure, whereby 2.8 g of (2S)-2-amino-4-benzylthiobutanoic acid was obtained in a yield of 86%.

5.6 ml (44 mmol) of chlorotrimethylsilane was added to an anhydrous tetrahydrofuran solution of 0.49 g (22 mmol) of lithium boron hydride, and the mixture was stirred at room temperature for 30 minutes. To this mixture, 2.5 g (11 mmol) of the above prepared (2S)-2-amino-4-benzylthiobutanoic acid was added, and the thus obtained reaction mixture was stirred overnight at room temperature. Methanol was added to the reaction mixture, and then the solvent was distilled away therefrom under reduced pressure.

The residue thus obtained was dissolved in a 1 N sodium hydroxide aqueous solution, and extracted with chloroform. The extract layer was dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure, whereby 2.0 g of the captioned Reference Compound No. 3-31 was obtained in a yield of 85.5%.

NMR (δ, $CDCl_3$): 7.22 - 7.32 (m, 5H), 3.72 (s, 2H), 3.51 - 3.56 (m, 1H), 3.26 - 3.30 (m, 1H), 2.90 - 3.00 (m, 1H), 2.42 - 2.56 (m, 2H), 2.00 - 2.12 (m, 1H), 1.62 - 1.73 (m, 1H), 1.48 - 1.58 (m, 1H)

Reference Example 3-32

Synthesis of (2S)-2-amino-4-(2-fluorobenzylthio)butanol (Reference Compound No. 3-32):

The same reaction procedure as used in Reference Example 3-31 was repeated except that the benzyl bromide used in Reference Example 3-31 was replaced by 2-fluorobenzyl bromide, whereby the captioned Reference Compound No. 3-32 was obtained.

NMR (δ, $CDCl_3$): 7.31 - 7.36 (m, 1H), 7.19 - 7.27 (m, 1H), 7.00 - 7.12 (m, 2H), 3.75 (s, 2H), 3.55 (dd, J=10.68Hz, J=3.96Hz, 1H), 3.28 (dd, J=13.59Hz, J=7.49Hz, 1H), 2.89 - 2.97 (m, 1H), 2.47 - 2.62 (m, 2H), 1.98 (brs, 3H), 1.65 - 1.76 (m, 1H), 1.49 - 1.59 (m, 1H)

Reference Example 3-33

Synthesis of (2S)-2-amino-4-(2-chlorobenzylthio)butanol (Reference Compound No. 3-33):

The same reaction procedure as used in Reference Example 3-31 was repeated except that the benzyl bromide used in Reference Example 3-31 was replaced by 2-chlorobenzyl chloride, whereby the captioned Reference Compound No. 3-33 was obtained.

NMR (δ, $CDCl_3$): 7.33 - 7.39 (m, 2H), 7.19 - 7.26 (m, 2H), 3.84 (s, 2H), 3.57 (dd, J=10.69Hz, J=4.01Hz, 1H), 3.29 (dd, J=10.69Hz, J=7.49Hz, 1H), 2.93 - 3.01 (m, 1H), 2.50 - 2.66 (m, 2H), 2.04 (brs, 3H), 1.66 - 1.78 (m, 1H), 1.50 - 1.62 (m, 1H)

Reference Example 3-34

Synthesis of (2S)-2-amino-4-(2-fluorophenylthio)butanol hydrochloride (Reference Compound No. 3-34):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and 2-fluorothiophenol, so that L-N-(t-butoxycarbonyl)-S-(2-fluorophenyl)homocysteine benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.18 - 7.42 (m, 6H), 7.01 - 7.07 (m, 2H), 5.16 (d, J=2.66Hz, 2H), 5.09 - 5.14 (m, 1H), 4.45 - 4.53 (m, 1H), 2.90 (t, J=7.49Hz, 2H), 2.06 - 2.18 (m, 1H), 1.86 - 1.98 (m, 1H), 1.43 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-34 was obtained.

Reference Example 3-35

Synthesis of (2S)-2-amino-4-(2-chlorophenylthio)butanol hydrochloride (Reference Compound No. 3-35):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and 2-chlorothiophenol, so that L-N-(t-butoxycarbonyl)-S-(2-chlorophenyl)homocysteine benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.34 (s, 6H), 7.08 - 7.23 (m, 3H), 5.17 (d, J=3.31Hz, 3H), 4.40 - 4.51 (m, 1H), 2.90 - 2.96 (m, 2H), 2.17 - 2.25 (m, 1H), 1.95 - 2.05 (m, 1H), 1.44 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-35 was obtained.

Reference Example 3-36

Synthesis of (2S)-2-amino-4-(4-chlorophenylthio)butanol hydrochloride (Reference Compound No. 3-36):

The same reaction procedure for preparation of the L-N-(t-butoxycarbonyl)-O-phenylhomoserine ethyl ester as used in Reference Example 3-24 was repeated except that the ethyl bromide and the phenol used in Reference Example 3-24 were respectively replaced by benzyl bromide and 4-chlorothiophenol, so that L-N-(t-butoxycarbonyl)-S-(4-chlorophenyl)homocysteine benzyl ester was obtained.

NMR (δ, $CDCl_3$): 7.29 - 7.37 (m, 4H), 7.21 (s, 5H), 5.15 (d, J=7.16Hz, 2H), 5.10 - 5.15 (m, 1H), 4.12 - 4.19 (m, 1H), 2.84 - 2.90 (m, 2H), 2.05 - 2.18 (m, 1H), 1.86 - 1.97 (m, 1H), 1.43 (s, 9H)

Subsequently, the same reaction procedure for preparation of the Reference Compound No. 3-24 as used in Reference Example 3-24 was repeated, whereby the captioned Reference Compound No. 3-36 was obtained.

Reference Example 3-37

Synthesis of L-N-[1-(benzyloxycarbonyl)-piperidine-4-carbonyl]leucine (Reference Compound No. 3-37):

2.58 g (25.5 mmol) of triethylamine, 6.7 g (25.5 mmol) of N-(benzyloxycarbonyl)-piperidine-4-carboxylic acid and 4.88 g (25.5 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride were successively added to 100 ml of a chloroform solution containing 5 g (25.5 mmol) of L-leucine ethyl ester hydrochloride with stirring under an ice-cooled condition. After the temperature of the mixture was raised to room temperature, the mixture was stirred overnight. The reaction mixture was washed successively with 1 N hydrochloric acid, a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, whereby 10.1 g of L-N-[1-(benzyloxycarbonyl)-piperidine-4-carbonyl]leucine ethyl ester was obtained in a yield of 98%.

With stirring under an ice-cooled condition, 10 ml of an aqueous solution containing 1.02 g (25.5 mmol) of sodium hydroxide was added to a methanol solution in which 10.1 g of the above prepared L-N-[1-(benzyloxycarbonyl)-piperidine-4-carbonyl]leucine ethyl ester was dissolved. This reaction mixture was further stirred for 3 hours.

The reaction mixture was concentrated under reduced pressure. The residue thus obtained was

dissolved in water and washed with ether twice. The resultant water layer was made acid (pH = 1) with the addition of concentrated hydrochloric acid, and then extracted with ethyl acetate twice. The extract layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby 9.3 g of the captioned Reference Compound No. 3-37 was obtained as an oily material in a yield of 96%.

NMR (δ, $CDCl_3$): 8.80 - 9.00 (m, 1H), 7.32 - 7.38 (m, 5H), 6.05 - 6.15 (m, 1H), 5.14 (s, 2H), 4.58 - 4.68 (m, 1H), 4.16 - 4.26 (m, 2H), 2.82 - 2.95 (m, 2H), 2.37 - 2.48 (m, 1H), 1.82 - 1.92 (m, 2H), 1.56 - 1.75 (m, 5H), 0.95 - 0.97 (m, 6H)

Reference Example 3-38

Synthesis of L-N-(N-phenylcarbamoyl)leucine (Reference Compound No. 3-38):

5.16 g (51 mmol) of triethylamine was added to 200 ml of a chloroform solution containing 5 g (25.5 mmol) of L-leucine ethyl ester hydrochloride with stirring under an ice-cooled condition. Subsequently, a chloroform solution containing 2.76 ml (25.5 mmol) of isocyanic acid phenyl ester was added dropwise to the above mixture. After stirring overnight, the reaction mixture was washed successively with 1 N hydrochloric acid, a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, whereby 5.85 g of L-N-(N-phenylcarbamoyl)leucine ethyl ester was obtained in a yield of 82%.

With stirring under an ice-cooled condition, 10 ml of an aqueous solution containing 1.848 g (46 mmol) of sodium hydroxide was added to 200 ml of a methanol solution in which 5.85 g of the above prepared L-N-(N-phenylcarbamoyl)leucine ethyl ester was dissolved. This reaction mixture was further stirred for 3 hours.

The reaction mixture was concentrated under reduced pressure. The residue thus obtained was dissolved in water and washed with ether twice. The resultant water layer was made acid (pH = 1) with the addition of concentrated hydrochloric acid, so that crystals were caused to separate out.

These crystals separated by filtration were washed successively with water, cooled ethanol and ether, and then dried, whereby 3.55 g of the captioned Reference Compound No. 3-38 was obtained in a yield of 6.7%.

Melting point (°C): 143.8 - 145.8

NMR (δ, CD_3OD): 7.33 (dd, J = 8.5Hz, 0.96Hz, 2H), 7.25 (t, J = 5.1Hz, 2H), 6.98 (td, J = 8.5Hz, 1.2Hz, 1H), 4.37 (dd, J = 9.3Hz, 5.1Hz, 1H), 1.51 - 1.89 (m, 3H), 0.99 (d, J = 3.2Hz, 3H), 0.97 (d, J = 3.0Hz, 3H)

Reference Example 3-39

Synthesis of L-N-(4-methylbenzenesulfonyl)leucine (Reference Compound No. 3-39):

The same reaction procedure as used in Reference Example 3-38 was repeated except that the 2.76 ml of isocyanic acid phenyl ester used in Reference Example 3-38 was replaced by 4.86 g of 4-methylbenzenesulfonyl chloride, whereby 6.2 g of the captioned Reference Compound No. 3-39 was obtained.

Melting point (°C): 117.2 - 120

NMR (δ, $CDCl_3$): 7.73 (d, J = 8.3Hz, 2H), 7.28 (d, J = 8.3Hz, 2H), 5.07 (d, J = 9.7Hz, 1H), 3.86 - 3.99 (m, 1H), 2.41 (s, 3H), 1.70 - 1.85 (m, 1H), 1.45 - 1.60 (m, 2H), 0.89 (d, J = 6.6Hz, 3H), 0.82 (d, J = 6.5Hz, 3H)

Reference Example 3-40

Synthesis of L-N-methyl-N-(benzyloxycarbonyl)leucine (Reference Compound No. 3-40):

With stirring under an ice-cooled condition, 10 ml of a benzene solution containing 0.982 ml (6.88 mmol) of benzyloxycarbonyl chloride and 10 ml of a 1 N sodium hydroxide aqueous solution were simultaneously added dropwise to 10 ml of a 1 N sodium hydroxide aqueous solution containing 1 g (6.88 mmol) of commercially available L-N-methylleucine. After the temperature of the reaction mixture was raised to room temperature, the reaction mixture was stirred overnight. The reaction mixture was washed with ether twice. The resultant water layer was made acid (pH = 1) with the addition of concentrated hydrochloric acid, and then extracted with ethyl acetate twice. The extract layer was dried over anhydrous sodium sulfate

and concentrated under reduced pressure, whereby 0.46 g of the captioned Reference Compound No. 3-40 was obtained.

NMR (δ, $CDCl_3$): 7.30 - 7.40 (m, 5H), 5.10 - 5.23 (m, 2H), 4.92 (t, J=8.3Hz, 2/3H), 4.77 (dd, J=10.5Hz, 4.5Hz, 1/3H), 2.88 (s, 3H), 1.45 - 1.82 (m, 3H), 0.86 - 1.05 (m, 6H)

Example 3-1

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-(1-formyl-2-benzyloxy)ethylamide (Compound No. 3-1):

With stirring under an ice-cooled condition, 784 mg (7.8 mmol) of triethylamine, 23 ml (8.5 mmol) of (L)-N-(benzyloxycarbonyl)leucine (hereinafter referred to as L-Cbz-Len-OH)•toluene solution and 1.18 g (7.8 mmol) of 1-hydroxybenzotriazole were successively added to 200 ml of a chloroform suspension of 2.01 g (7.8 mmol) of the Reference Compound No. 3-1 synthesized in Reference Example 3-1. Subsequently, 50 ml of a chloroform solution of 1.76 g (8.525 mmol) of dicyclohexylcarbodiimide was added dropwise to the above prepared mixture. This reaction mixture was stirred overnight at room temperature, and then, the insoluble components were removed therefrom by filtration. The thus obtained filtrate was washed successively with 1 N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated.

The residue thus obtained was chromatographed on a silica gel column for purification, whereby 2.74 g of L-N-(benzyloxycarbonyl)-leucyl-L-(O-benzyl)-serine ethyl ester was obtained in a yield of 75%.

182 mg (8.4 mmol) of lithium boron hydride was added to 50 ml of an anhydrous tetrahydrofuran solution containing 1.58 g (3.4 mmol) of the above prepared L-N-(benzyloxycarbonyl)-leucyl-L-(O-benzyl)-serine ethyl ester, with stirring under an ice-cooled condition. Then, 3 ml of methanol was added dropwise to the above mixture. After the mixture was further stirred for one hour, 10 ml of water was added dropwise to the mixture. Then, the reaction mixture was concentrated under reduced pressure.

The residue thus obtained was made acid (pH=1) with the addition of 1 N hydrochloric acid and extracted with methylene chloride twice. The extract organic layer was washed successively with a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated. The residue thus obtained was recrystallized from a mixed solvent of benzene and ethyl acetate, so that 0.965 g of a corresponding alcohol was obtained in a yield of 67%.

With stirring at room temperature, 10 ml of an anhydrous dimethyl sulfoxide solution containing 1.33 g (8.4 mmol) of sulfur trioxide•pyridine complex was added dropwise to 10 ml of an anhydrous dimethyl sulfoxide solution containing 900 mg (2.1 mmol) of the above prepared alcohol and 850 mg (8.4 mmol) of triethylamine. After stirred for 30 minutes, the reaction mixture was poured into iced water and extracted with ethyl acetate three times. The organic layer was washed successively with a 10% citric acid aqueous solution, water, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.425 g of the captioned Compound No. 3-1 was obtained as an oily material in a yield of 47%.

NMR (δ, $CDCl_3$): 9.56 (s, 1H), 7.25 - 7.36 (m, 10H), 6.75 - 6.95 (m, 1H), 5.20 - 5.22 (m, 1H), 5.11 (s, 2H), 4.55 - 4.59 (m, 1H), 4.43 - 4.50 (m, 2H), 4.25 - 4.35 (m, 1H), 3.99 - 4.03 (m, 1H), 3.66 - 3.70 (m, 1H), 1.49 - 1.73 (m, 3H), 0.92 - 0.95 (m, 6H)

R_f values: 0.19 (Developing Solvent A: mixture of hexane and ethyl acetate at a mixing ratio of 1:1)
0.14 (Developing Solvent B: mixture of methylene chloride and acetone at a mixing ratio of 10:1)

Example 3-2

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-(1-formyl-2-benzylthio)ethylamide (Compound No. 3-2):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by 2.2 g of commercially available L-S-benzylcysteine ethyl ester hydrochloride, whereby 0.14 g of the captioned Compound No. 3-2 was obtained.

Melting point (°C): 116.8 - 122.1

NMR (δ, $CDCl_3$): 9.49 (s; 1H), 7.28 - 7.34 (m, 10H), 6.72 - 6.79 (m, 1H), 5.11 (s, 2H), 5.17 - 5.20 (m, 2H), 4.48 - 4.57 (m, 1H), 4.20 - 4.28 (m, 1H), 3.71 (s, 2H), 2.88 (d, J=5.86Hz, 2H), 1.48 - 1.75 (m, 3H), 0.95 (d, J=5.97Hz, 6H)

R_f values: 0.35 (Developing Solvent A)
0.25 (Developing Solvent B)

Example 3-3

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(2-phenylethylthio)]ethylamide (Compound No. 3-3):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 3.3 g of Reference Compound No. 3-2 synthesized in Reference Example 3-2, whereby 0.57 g of the captioned Compound No. 3-3 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.57 (s, 1H), 7.18 - 7.36 (m, 10H), 6.90 - 7.00 (m, 1H), 5.15 - 5.20 (m, 1H), 5.10 (s, 2H), 4.48 - 4.55 (m, 1H), 4.24 - 4.27 (m, 1H), 2.77 - 2.96 (m, 6H), 1.49 - 1.71 (m, 3H), 0.92 - 0.95 (m, 6H)

R_f values: 0.30 (Developing Solvent A)
0.23 (Developing Solvent B)

Example 3-4

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(3-phenylpropylthio)]ethylamide (Compound No. 3-4):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 3.47 g of Reference Compound No. 3-3 synthesized in Reference Example 3-3, whereby 0.79 g of the captioned Compound No. 3-4 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.59 (brs, 1H), 7.28 - 7.36 (m, 8H), 7.15 - 7.21 (m, 2H), 6.90 - 7.00 (m, 1H), 5.11 (s, 2H), 5.10 - 5.20 (m, 1H), 4.50 - 4.58 (m, 1H), 4.22 - 4.30 (m, 1H), 2.95 (brs, 2H), 2.69 (t, J=7.33Hz, 2H), 2.53 (t, J=7.32Hz, 2H), 1.84 - 1.94 (m, 2H), 1.48 - 1.70 (m, 3H), 0.94 (d, J=6.73Hz, 6H)

R_f values: 0.31 (Developing Solvent A)
0.26 (Developing Solvent B)

Example 3-5

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-2-(3-phenylpropyloxy)]ethylamide (Compound No. 3-5):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 1.13 g of Reference Compound No. 3-4 synthesized in Reference Example 3-4, whereby 0.315 g of the captioned Compound No. 3-5 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.57 (s, 1H), 7.25 - 7.36 (m, 8H), 7.14 - 7.21 (m, 2H), 6.77 - 6.93 (m, 1H), 5.20 - 5.28 (m, 1H), 5.05 - 5.14 (m, 2H), 4.54 - 4.59 (m, 1H), 4.27 - 4.32 (m, 1H), 3.94 - 3.98 (m, 1H), 3.61 - 3.65 (m, 1H), 3.41 (t, J=6.35Hz, 2H), 2.62 (t, J=7.92Hz, 2H), 1.79 - 1.90 (m, 2H), 1.51 - 1.79 (m, 3H), 0.93 - 0.96 (m, 6H)

R_f values: 0.18 (Developing Solvent A)
0.16 (Developing Solvent B)

Example 3-6

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-2-(thiophene-3-ylmethyl)oxy]ethylamide (Compound No. 3-6):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 1.20 g of Reference Compound No. 3-5 synthesized in Reference Example 3-5, whereby 0.33 g of the captioned Compound No. 3-6 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.55 (s, 1H), 7.26- 7.34 (m, 6H), 7.18 (s, 1H), 6.97 - 7.05 (m, 1H), 6.70 - 6.93 (m, 1H), 5.12 (s, 2H), 5.10 - 5.20 (m, 1H), 4.53 - 4.60 (m, 1H), 4.49 (s, 2H), 4.22 - 4.31 (m, 1H), 3.97 - 4.05 (m, 1H), 3.65 - 3.72 (m, 1H), 1.50 - 1.75 (m, 3H), 0.95 (t, J=4.45Hz, 6H)
R_f values:	0.21 (Developing Solvent A)
	0.24 (Developing Solvent B)

Example 3-7

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-(1-formyl-2-diphenylmethylthio)ethylamide (Compound No. 3-7):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 1.13 g of Reference Compound No. 3-6 synthesized in Reference Example 3-6, whereby 0.17 g of the captioned Compound No. 3-7 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.44 (s, 1H), 7.21 - 7.41 (m, 15H), 6.72 - 6.85 (m, 1H), 5.08 - 5.18 (m, 4H), 4.46 - 4.51 (m, 1H), 4.20 - 4.30 (m, 1H), 2.75 - 2.92 (m, 2H), 1.47 - 1.71 (m, 3H), 0.93 - 0.95 (m, 6H)
R_f values:	0.32 (Developing Solvent A)
	0.25 iDeveloping Solvent B)

Example 3-8

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-(1-formyl-2-cyclohexylmethylthio)ethylamide (Compound No. 3-8):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 2.53 g of Reference Compound No. 3-7 synthesized in Reference Example 3-7, whereby 0.74 g of the captioned Compound No. 3-8 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.61 (s, 1H), 7.35 (s, 5H), 6,89 - 6.93 (m, 1H), 5.12 (s, 2H), 5.10 - 5.20 (s, 1H), 4.51 - 4.57 (m, 1H), 4.22 - 4.30 (m, 1H), 2.92 - 2.98 (m, 2H), 2.42 (d, J=6,84Hz, 2H), 1.28 - 1.82 (m, 10H), 1.11 - 1.26 (m, 4H), 0.95 (d, J=6.02Hz, 6H)
R_f values:	0.38 (Developing Solvent A)
	0.28 (Developing Solvent B)

Example 3-9

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-(1-formyl-2-cyclopentylthio)ethylamide (Compound No. 3-9):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 2.0 g of Reference Compound No. 3-8 synthesized in Reference Example 3-8, whereby 0.29 g of the captioned Compound No. 3-9 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.62 (s, 1H), 7.35 (S, 5H), 6.89 - 6.92 (m, 1H), 5.12 (s, 2H), 5.10 - 5.20 (m, 1H), 4.55 - 4.60 (m, 1H), 4.32 - 4.41 (m, 1H), 2.90 - 3.12 (m, 3H), 1.95 - 2.05 (m, 3H), 1.46 - 1.72 (m, 8H), 0.95 (d, J=5.26Hz, 6H)
R_f values:	0.37 (Developing Solvent A)
	0.32 (Developing Solvent B)

Example 3-10

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(thiophene-2-ylmethyl)thio]ethylamide (Compound No. 3-10):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 0.96 g of Reference Compound No. 3-9 synthesized in Reference Example 3-9, whereby 0.22 g of the captioned Compound No. 3-10 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.50 (s, 1H), 7.34 (s, 5H), 7.21 - 7.23 (m, 1H), 6.89 - 6.96 (m, 2H), 6.79 - 6.83 (m, 1H), 5.12 (s, 2H), 5.11 - 5.17 (m, 1H), 4.48 - 4.53 (m, 1H), 4.21 - 4.30 (m, 1H), 3.92 (s, 2H), 2.94 (d, J=5.76, 2H), 1.49 - 1.72 (m, 3H), 0.95 (d, J=6.08Hz, 6H)

R_f values: 0.28 (Developing Solvent A)
0.18 (Developing Solvent B)

Example 3-11

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(thiophene-3-ylmethyl)thio]ethylamide (Compound No. 3-11):

The same reaction procedure as used in Example 3-1 was repeated except that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by the 2.5 g of Reference Compound No. 3-10 synthesized in Reference Example 3-10, whereby 1.49 g of the captioned Compound No. 3-11 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.49 (s, 1H), 7.26 - 7.34 (m, 6H), 7.16 (s, 1H), 7.05 (d, J=4.93, 1H), 6.79 - 6.91 (m, 1H), 5.14 - 5.18 (m, 1H), 5.12 (s, 2H), 4.48 - 4.52 (m, 1H), 4.20 - 4.30 (m, 1H), 3.73 (s, 2H), 2.86 (brs, 2H), 1.49 - 1.71 (m, 3H), 0.95 (d, J=5.96Hz, 6H)

R_f values: 0.33 (Developing Solvent A)
0.22 (Developing Solvent B)

Example 3-12

Synthesis of L-N-[1-(benzyloxycarbonyl)-piperidine-4-carbonyl]leucine-(2R)-(1-formyl-2-benzylthio)-ethylamide (Compound No. 3-12):

The same reaction procedure as used in Example 3-1 was repeated except that L-cbz-Len-OH used in Example 3-1 was replaced by the Reference Compound No. 3-37 synthesized in Reference Example 3-38, and that the 2.01 g of Reference Compound No. 3-1 synthesized in Reference Example 3-1 used in Example 3-1 was replaced by 0.98 g of commercially available L-S-benzylcysteine ethyl ester hydrochloride, whereby 0.39 g of the captioned Compound No. 3-12 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.46 (s, 1H), 7.24 - 7.36 (m, 10H), 6.25 - 6.40 (m, 1H), 5.11 (s, 2H), 4.56 - 4.59 (m, 1H), 4.42 - 4.47 (m, 1H), 4.10 - 4.25 (m, 2H), 3.70 (d, J=3.27Hz, 2H), 2.74 - 2.91 (m, 4H), 2.25 - 2.33 (m, 1H), 1.52 - 1.82 (m, 8H), 0.93 (t, J=5.58Hz, 6H)

R_f values: 0.04 (Developing Solvent A)
0.05 (Developing Solvent B)

Example 3-13

Synthesis of L-N-(benzyloxycarbonyl)leucine-(2R)-[1-formyl-2-(naphthalene-1-ylmethylthio)]ethylamide (Compound No. 3-13):

With stirring under an ice-cooled condition, 0.81 g (3.98 mmol) of triethylamine was added dropwise to a chloroform solution containing the 1.25 g (3.98 mmol) of Reference Compound No. 3-11 synthesized in Reference Example 3-11 and 1.45 g (3.98 mmol) of L-N-(benzyloxycarbonyl)leucine N-hydroxysuccinimide ester. This reaction mixture was further stirred overnight. The reaction mixture was washed successively with 1 N hydrochloric acid aqueous solution, a saturated aqueous solution of sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate. The solvent was distilled away from the reaction mixture under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.9 g of L-N-(benzyloxycarbonyl)-leucyl-(L)-S-(naphthalene-1-yl-methyl)cysteine ethyl ester was obtained in a yield of 42%.

To an anhydrous tetrahydrofuran solution of 0.9 g (1.68 mmol) of the above prepared ester, 0.073 g (3.35 mmol) of lithium boron hydride was added, and then methanol was added dropwise under an ice-cooled condition. This reaction mixture was stirred for 3 hours. After stirring, water was added dropwise to the reaction mixture and the solvent was distilled away therefrom under reduced pressure.

An aqueous solution of the thus obtained residue was made acid with the addition of a 1 N hydrochloric acid aqueous solution, and extracted with ethyl acetate. The extract layer was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, and the residue thus obtained was chromatographed on a silica gel column for purification, so that 0.577 g of an alcohol was obtained in a yield of 69%.

A dimethyl sulfoxide solution of 0.708 g (4.44 mmol) of sulfur trioxide•pyridine complex was added dropwise to an anhydrous dimethyl sulfoxide solution containing 0.55 g (1.11 mmol) of the above prepared alcohol and 0.45 g (4.44 mmol) of triethylamine with stirring at room temperature. This reaction mixture was further stirred at room temperature for one hour. The reaction mixture was poured into iced water, and extracted with ethyl acetate three times. The extract layer was washed successively with a 10% citric acid aqueous solution, a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. The solvent was distilled away under reduced pressure, and the residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.26 g of the captioned Compound No. 3-13 was obtained in a yield of 47%.

Melting point (°C):	115.0 - 128.1 (dec.)
NMR (δ, $CDCl_3$):	9.46 (s, 1H), 8.06 (d, J=7.92Hz, 1H), 7.86 (d, J=9.23, 1H), 7.76 - 7.80 (m, 2H), 7.31 - 7.58 (m, 8H), 6.75 - 6.90 (m, 1H), 5.08 (d, J=3.78Hz, 2H), 4.98 - 5.05 (m, 1H), 4.48 - 4.58 (m, 1H), 4.17 - 4.27 (m, 1H), 4.17 (s, 2H), 2.90 - 2.93 (m, 2H), 1.35 - 1.72 (m, 3H), 0.91 - 0.93 (m, 6H)
R_f values:	0.28 (Developing Solvent A) 0.22 (Developing Solvent B)

Example 3-14

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(naphthalene-2-ylmethyl)thio]ethylamide (Compound No. 3-14):

The same reaction procedure as used in Example 3-13 was repeated except that the 1.25 g of Reference Compound No. 3-11 synthesized in Reference Example 3-11 was replaced by the 1.26 g of Reference Compound No. 3-12 synthesized in Reference Example 3-12, whereby 0.1 g of the captioned Compound No. 3-14 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.48 (d, J=5.10Hz, 1H), 7.71 - 7.83 (m, 3H), 7.32 - 7.49 (m, 9H), 6.80 - 6.82 (m, 1H), 5.11 (d, J=3.36Hz, 2H), 5.07 - 5.18 (m, 1H), 5.50 - 5.57 (m, 1H), 4.22 - 4.30 (m, 1H), 3.87 (s, 2H), 2.87 (d, J=5.01Hz, 2H), 1.45 - 1.80 (m, 3H), 0.93 (d, J=6.36Hz, 6H)
R_f values:	0.29 (Developing Solvent A) 0.22 (Developing Solvent B)

Example 3-15

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(2-chlorobenzyl)thio]ethylamide (Compound No. 3-15):

The same reaction procedure as used in Example 3-13 was repeated except that the 1.25 g of Reference Compound No. 3-11 synthesized in Reference Example 3-11 was replaced by the 1.24 g of Reference Compound No. 3-13 synthesized in Reference Example 3-13, whereby 0.57 g of the captioned Compound No. 3-15 was obtained.

Melting point (°C):	128.6 - 131.9
NMR (δ, $CDCl_3$):	9.55 (s, 1H), 7.20 - 7.40 (m, 9H), 6.83 - 6.91 (m, 1H), 5.10 - 5.20 (brs, 3H), 4.52 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 3.84 (s, 2H), 2.93 (brs, 2H), 1.49 - 1.73 (m, 4H), 0.95 (d, J=4.29Hz, 6H)
R_f values:	0.31 (Developing Solvent A) 0.24 (Developing Solvent B)

Example 3-16

Synthesis of L-N-methyl-N-(benzyloxycarbonyl)leucine-(L)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide (Compound No. 3-16):

A chloroform solution of 0.684 g (3.22 mmol) of dicyclohexylcarbodiimide was added dropwise to 100 ml of a chloroform solution containing the 0.9 g (3.22 mmol) of Reference Compound No. 3-40 synthesized in Reference Example 3-40, 0.326 g (3.22 mmol) of triethylamine, 0.443 g (3.22 mmol) of 1-hydroxybenzotriazole and the 0.748 g (3.22 mmol) of Reference Compound No. 3-16 synthesized in Reference Example 3-16, with stirring in an ice bath containing salt. This reaction mixture was further stirred overnight.

The insoluble components were removed from the reaction mixture by filtration. The filtrate thus obtained was washed successively with 1 N hydrochloric acid, a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 1.2 g of L-N-methyl-N-(benzyloxycarbonyl)leucine-(L)-[1-hydroxymethyl-2-(4-chlorophenyl)]ethylamide was obtained in a yield of 75%.

10 ml of an anhydrous dimethyl sulfoxide solution of 1.14 g (7.22 mmol) of sulfur trioxide•pyridine complex was added dropwise to 10 ml of an anhydrous dimethyl sulfoxide solution containing 0.89 g (1.8 mmol) of the above prepared L-N-methyl-N-(benzyloxycarbonyl)leucine-(2R)-[1-hydroxymethyl-2-(4-chlorophenyl)]ethylamide and 0.13 g (7.22 mmol) of triethylamine with stirring at room temperature. This reaction mixture was further stirred for 30 minutes. The reaction mixture was poured into iced water, and extracted with ethyl acetate three times. The extract organic layer was washed successively with a 10% citric acid aqueous solution, water, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 0.52 g of the captioned Compound No. 3-16 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.50 (s, 1H), 7.15 - 7.40 (m, 9H), 6.80 - 6.95 (m, 1H), 5.10 - 5.30 (m, 2H), 4.60 - 4.90 (m, 1H), 4.40 - 4.55 (m, 1H), 3.60 - 3.71 (m, 2H), 2.85 (s, 3H), 2.60 - 2.85 (m, 2H), 1.60 - 1.80 (m, 2H), 1.42 - 1.60 (m, 1H), 0.80 - 1.05 (m, 6H)

R_f values: 0.42 (Developing Solvent A)
0.30 (Developing Solvent B)

Example 3-17

Synthesis of L-N-(N-phenylcarbamoyl)leucine-(2R)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide (Compound No. 3-17):

The same reaction procedure as used in Example 3-16 was repeated except that the 0.9 g of Reference Compound No. 3-40 synthesized in Reference Example 3-40 was replaced by the 1.0 g of Reference Compound No. 3-38 synthesized in Reference Example 3-38, whereby 0.34 g of the captioned Compound No. 3-17 was obtained as an amorphous material.

NMR (δ, $CDCl_3$): 9.40 (s, 1H), 7.97 (bs, 1H), 7.05 - 7.45 (m, 9H), 6.63 (bs, 1H), 4.50 - 4.60 (m, 1H), 4.30 - 4.40 (m, 1H), 3.60 - 3.75 (m, 2H), 3.10 - 3.30 (m, 2H), 1.45 - 1.85 (m, 3H), 0.85 - 1.10 (m, 6H)

R_f values: 0.20 (Developing Solvent A)
0.10 (Developing Solvent B)

Example 3-18

Synthesis of L-N-(4-methylbenzenesulfonyl)leucine-(2R)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide (Compound No. 3-18):

The same reaction procedure as used in Example 3-16 was repeated except that the 0.9 g of Reference Compound No. 3-40 synthesized in Reference Example 3-40 was replaced by the 1.0 g of Reference Compound No. 3-39 synthesized in Reference Example 3-39, whereby 0.54 g of the captioned Compound No. 3-18 was obtained as an amorphous material.

NMR (δ, $CDCl_3$): 9.37 (s, 1H), 7.73 (d, J = 8.2Hz, 2H), 7.20 - 7.35 (m, 6H), 6.61 (d, J = 8.4Hz, 1H), 4.99 (d, J = 5.8Hz, 1H), 4.29 - 4.45 (m, 2H), 3.63 (s, 2H), 2.70 - 2.90 (m, 2H), 2.40 (s, 3H),

	1.40 - 1.70 (m, 3H), 0.90 - 1.10 (m, 6H)
R_f values:	0.33 (Developing Solvent A)
	0.25 (Developing Solvent B)

Example 3-19

Synthesis of L-N-(benzyloxycarbonyl)phenylalanine-(2R)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide (Compound No. 3-19):

The same reaction procedure as used in Example 3-16 was repeated except that the 0.9 g of Reference Compound No. 3-40 synthesized in Reference Example 3-40 was replaced by 1.0 g of commercially available L-N-(benzyloxycarbonyl)phenylalanine, whereby 0.4 g of the captioned Compound No. 3-19 was obtained.

Melting point (°C):	129.4 - 133.4
NMR (δ, $CDCl_3$):	9.38 (s, 1H), 7.10 - 7.41 (m, 14H), 6.30 - 6.40 (m, 1H), 5.20 - 5.30 (m, 1H), 5.09 (s, 2H), 4.35 - 4.51 (m, 2H), 3.35 - 3.45 (m, 2H), 3.00 - 3.20 (m, 2H), 2.70 - 2.80 (m, 2H)
R_f values:	0.36 (Developing Solvent A)
	0.24 (Developing Solvent B)

Example 3-20

Synthesis of L-N-(benzyloxycarbonyl)-valine-(2R)-[1-formyl-2-(4-chlorobenzylthio)]ethylamide (Compound No. 3-20):

The same reaction procedure as used in Example 3-16 was repeated except that the 0.9 g of Reference Compound No. 3-40 synthesized in Reference Example 3-40 was replaced by 1.0 g of commercially available L-N-(benzyloxycarbonyl)valine, whereby 0.14 g of the captioned Compound No. 3-20 was obtained.

Melting point (°C):	126.2 - 128.7
NMR (δ, $CDCl_3$):	9.52 (s, 1H), 7.20 - 7.45 (m, 9H), 6.60 - 6.75 (m, 1H), 5.25 - 5.35 (m, 1H), 5.11 (s, 2H), 4.50 - 4.61 (m, 1H), 4.00 - 4.15 (m, 1H), 3.68 (s, 2H), 2.75 - 2.90 (m, 2H), 2.10 - 2.25 (m, 1H), 0.90 - 1.05 (m, 6H)
R_f values:	0.36 (Developing Solvent A)
	0.21 (Developing Solvent B)

Example 3-21

Synthesis of L-N-(benzyloxycarbonyl)leucine-(2R)-[1-formyl-2-(4-chlorobenzyl)thio]ethylamide (Compound No. 3-21):

6.25 g (17.26 mmol) of L-N-(benzyloxycarbonyl)leucine-N-hydroxysuccinimide ester was gradually added to 200 ml of a chloroform solution containing the 4 g (17.26 mmol) of Reference Compound No. 3-16 synthesized in Reference Example 3-16 and 1.74 g (17.26 mmol) of triethylamine with stirring under an ice-cooled condition. After the temperature of the reaction mixture was raised to room temperature, the mixture was stirred overnight.

The reaction mixture was washed successively with 1 N hydrochloric acid, a saturated solution of sodium hydrogencarbonate (three times) and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, so that 7.8 g of L-N-(benzyloxycarbonyl)leucine-(2R)-[1-hydroxymethyl-2-(4-chlorobenzylthio)]ethylamide was obtained in a yield of 94%.

30 ml of an anhydrous dimethyl sulfoxide solution of 10.34 g (65 mmol) of sulfur trioxide•pyridine complex was added dropwise to 100 ml of an anhydrous dimethyl sulfoxide solution containing 7.8 g (16.28 mmol) of the above prepared L-N-(benzyloxycarbonyl)leucine-(2R)-[1-hydroxymethyl-2-(4-chlorobenzylthio)]-ethylamide and 6.57 g (65 mmol) of triethylamine with stirring at room temperature. This reaction mixture was further stirred for 30 minutes. The reaction mixture was poured into iced water, and extracted with ethyl acetate three times. The extract organic layer was washed successively with a 10% citric acid aqueous solution, water, a saturated solution of sodium hydrogencarbonate and a saturated aqueous solution of

sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column for purification, whereby 2.4 g of the captioned Compound No. 3-21 was obtained.

Melting point (°C):	116.0 - 130.7 (dec.)
NMR (δ, $CDCl_3$):	9.52 (d, J=4.88Hz, 1H), 7.22 - 7.33 (m, 10H), 6.83 - 6.91 (m, 1H), 5.11 (d, J=2.33Hz, 3H), 4.50 - 4.59 (m, 1H), 4.23 - 4.30 (m, 1H), 3.67 (s, 2H), 2.85 (d, J=4.99Hz, 2H), 1.49 - 1.72 (m, 3H), 0.94 - 0.96 (m, 6H)
R_f values:	0.25 (Developing Solvent A)
	0.19 (Developing Solvent B)

Example 3-22

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(3-chlorobenzyl)thio]ethylamide (Compound No. 3-22):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 3.0 g of Reference Compound No. 3-15 synthesized in Reference Example 3-15, whereby 0.68 g of the captioned Compound No. 3-22 was obtained.

Melting point (°C):	97.6 - 103.3
NMR (δ, $CDCl_3$):	9.53 (s, 1H), 7.16 - 7.34 (m, 9H), 6.84 - 6.90 (m, 1H), 5.11 (s, 2H), 5.10 - 5.17 (m, 1H), 4.50 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 3.68 (s, 2H), 2.80 - 2.93 (m, 2H), 1.48 - 1.76 (m, 3H), 0.94 - 0.97 (m, 6H)
R_f values:	0.25 (Developing Solvent A)
	0.18 (Developing Solvent B)

Example 3-23

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(2-fluorobenzyl)thio]ethylamide (Compound No. 3-23):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 8.7 g of Reference Compound No. 3-14 synthesized in Reference Example 3-14, whereby 2.75 g of the captioned Compound No. 3-23 was obtained.

Melting point (°C):	110.1 - 118.3
NMR (δ, $CDCl_3$):	9.54 (s, 1H), 7.08 - 7.34 (m, 7H), 7.02 - 7.12 (m, 2H), 6.83 (brs, 1H), 5.11 (s, 3H), 4.50 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 3.75 (d, J=2.93Hz, 2H), 2.93 (d, J=5.48Hz, 2H), 1.50 - 1.75 (m, 3H), 0.95 (d, J=6.18Hz, 6H)
R_f values:	0.30 (Developing Solvent A)
	0.22 (Developing Solvent B)

Example 3-24

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(3-fluorobenzyl)thio]ethylamide (Compound No. 3-24):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 6.5 g of Reference Compound No. 3-17 synthesized in Reference Example 3-17, whereby 0.37 g of the captioned Compound No. 3-24 was obtained.

Melting point (°C)	: 111.8 - 116.6
NMR (δ, $CDCl_3$):	9.53 (s, 1H), 7.24 - 7.34 (m, 6H), 7.06 (t, J=8.19Hz, 1H), 6.95 (t, J=8.96Hz, 1H), 6.81 - 6.87 (m, 1H), 5.11 (s, 3H), 4.50 - 4.59 (m, 1H), 4.21 - 4.30 (m, 1H), 3.70 (s, 7H), 2.87 (d, J=5.37Hz, 2H), 1.45 - 1.73 (m, 3H), 0.94 - 0.97 (m, 6H)
R_f values:	0.23 (Developing Solvent A)
	0.19 (Developing Solvent B)

Example 3-25

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(4-fluorobenzyl)thio]ethylamide (Compound No. 3-25):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 6.46 g of Reference Compound No. 3-18 synthesized in Reference Example 3-18, whereby 0.8 g of the captioned Compound No. 3-25 was obtained.

Melting point (°C):	71.2 - 76.3
NMR (δ, $CDCl_3$):	9.52 (d, J=5.37Hz, 1H), 7.25 - 7.34 (m, 7H), 6.95 - 7.07 (m, 2H), 6.82 - 6.90 (m, 1H), 5.11 - 5.20 (m, 3H), 4.50 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 3.69 (s, 2H), 2.80 - 2.90 (m, 2H), 1.49 - 1.73 (m, 3H), 0.95 (d, J=4.12Hz, 6H)
R_f values:	0.25 (Developing Solvent A)
	0.20 (Developing Solvent B)

Example 3-26

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(2-methoxybenzyl)thio]ethylamide (Compound No. 3-26):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 5.0 g of Reference Compound No. 3-19 synthesized in Reference Example 3-19, whereby 0.88 g of the captioned Compound No. 3-26 was obtained.

Melting point (°C):	110.8 - 120.2
NMR (δ, $CDCl_3$):	9.51 (s, 1H), 7.22 - 7.34 (m, 7H), 6.88 - 6.97 (m, 2H), 6.80 - 6.85 (m, 1H), 5.15 - 5.25 (m, 1H), 5.11 (s, 2H), 4.51 - 4.59 (m, 1H), 4.22 - 4.28 (m, 1H), 3.83 (s, 3H), 3.85 (d, J=5.42Hz, 1H), 3.74 (d, J=5.7Hz, 1H), 2.91 (d, J=5.86Hz, 2H), 1.42 - 1.74 (m, 3H), 0.93 - 0.96 (m, 6H)
R_f values:	0.27 (Developing Solvent A)
	0.20 (Developing Solvent B)

Example 3-27

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(3-methoxybenzyl)thio]ethylamide (Compound No. 3-27):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 3.41 g of Reference Compound No. 3-20 synthesized in Reference Example 3-20, whereby 0.71 g of the captioned Compound No. 3-27 was obtained.

Melting point (°C):	113.8 - 117.8
NMR (δ, $CDCl_3$):	9.50 (s, 1H), 7.20 - 7.34 (m, 6H), 6.76 - 6.90 (m, 4H), 4.49 - 4.53 (m, 1H), 4.23 - 4.30 (m, 1H), 3.80 (s, 3H), 3.68 (s, 2H), 2.88 (d, J=5.75Hz, 2H), 1.50 - 1.75 (m, 3H), 0.95 (d, J=5.97Hz, 6H)
R_f values:	0.25 (Developing Solvent A)
	0.19 (Developing Solvent B)

Example 3-28

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(4-methoxybenzyl)thio]ethylamide (Compound No. 3-28):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 4.54 g of Reference Compound No. 3-21 synthesized in Reference Example 3-21, whereby 0.13 g of the captioned Compound No. 3-28 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.45 (brs, 1H), 7.30 - 7.35 (m, 5H), 7.22 (d, J=8.57Hz, 2H), 6.85 (d, J=7.54Hz, 2H), 6.76 - 6.89 (m, 1H), 5.11 (s, 2H), 5.08 - 5.18 (m, 1H), 4.45 - 4.52 (m, 1H), 4.20 - 4.30 (m, 1H), 3.79 (s, 3H), 2.78 - 2.89 (m, 2H), 1.46 - 1.85 (m, 3H), 0.94 (d, J=5.86Hz, 6H)
R_f values:	0.19 (Developing Solvent A) 0.26 (Developing Solvent B)

Example 3-29

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(3-nitrobenzyl)thio]ethylamide (Compound No. 3-29):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 4.16 g of Reference Compound No. 3-22 synthesized in Reference Example 3-22, whereby 0.37 g of the captioned Compound No. 3-29 was obtained.

Melting point (°C):	72.9 - 104.9 (dec.)
NMR (δ, $CDCl_3$):	9.56 (d, J=6.95Hz, 1H), 8.21 (s, 1H), 8.13 (dd, J=2.44Hz, 7.22Hz, 1H), 7.65 (d, J=7.43Hz), 7.45 - 7.52 (m, 1H), 7.33 (d, J=4.1Hz, 5H), 6.91 - 7.07 (m, 1H), 5.20 (d, J=7.70Hz, 1H), 5.11 (d, J=5.48Hz, 2H), 4.53 - 4.59 (m, 1H), 4.20 - 4.35 (m, 1H), 3.80 (s, 2H), 2.80 - 2.95 (m, 2H), 1.51 - 1.80 (m, 3H), 0.95 (d, J=5.68Hz, 6H)
R_f values:	0.17 (Developing Solvent A) 0.17 (Developing Solvent B)

Example 3-30

Synthesis of L-N-benzyloxycarbonylleucine-(2R)-[1-formyl-2-(4-nitrobenzyl)thio]ethylamide (Compound No. 3-30):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 2.17 g of Reference Compound No. 3-23 synthesized in Reference Example 3-23, whereby 0.1 g of the captioned Compound No. 3-30 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.56 (s, 1H), 8.15 - 8.20 (m, 2H), 7.47 - 7.51 (m, 2H), 7.30 - 7.34 (m, 5H), 6.84 - 7.00 (m, 1H), 5.05 - 5.15 (m, 3H), 4.53 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 3.79 (s, 2H), 2.87 (d, J=5.26Hz, 2H), 1.49 - 1.75 (m, 3H), 0.94 - 0.97 (m, 6H)
R_f values:	0.15 (Developing Solvent A) 0.15 (Developing Solvent B)

Example 3-31

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-(1-formyl-3-phenyloxy)propylamide (Compound No. 3-31):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 0.52 g of Reference Compound No. 3-24 synthesized in Reference Example 3-24, whereby 0.52 g of the captioned Compound No. 3-31 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.64 (s, 1H), 7.24 - 7.33 (m, 8H), 6.82 - 6.98 (m, 3H), 4.95 - 5.15 (m, 3H), 4.55 - 4.59 (m, 1H), 4.20 - 4.30 (m, 1H), 3.95 - 4.10 (m, 2H), 2.27 - 2.53 (m, 2H), 1.45 - 1.72 (m, 3H), 0.92 (t, J=6.24Hz, 6H)
R_f values:	0.28 (Developing Solvent A) 0.19 (Developing Solvent B)

Example 3-32

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-(1-formyl-3-phenylthio)propylamide (Compound No. 3-32):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 0.87 g of Reference Compound No. 3-25 synthesized in Reference Example 3-25, whereby 0.42 g of the captioned Compound No. 3-32 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.52 (d, J=6.24Hz, 1H), 7.12 - 7.38 (m, 10H), 6.71 - 6.86 (m, 1H), 5.14 - 5.16 (d, J=6.95Hz, 1H), 5.10 (s, 2H), 4.51 - 4.59 (m, 1H), 4.20 - 4.25 (m, 1H), 2.91 - 2.96 (m, 2H), 2.25 - 2.35 (m, 1H), 1.85 - 2.00 (m, 1H), 1.48 - 1.72 (m, 3H), 0.92 - 0.98 (m, 6H)

R_f values: 0.31 (Developing Solvent A)
0.24 (Developing Solvent B)

Example 3-33

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-2-(2-chlorobenzyl)oxy]ethylamide (Compound No. 3-33):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 0.55 g of Reference Compound No. 3-26 synthesized in Reference Example 3-26, whereby 0.50 g of the captioned Compound No. 3-33 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.61 (s, 1H), 7.23 - 7.36 (m, 9H), 6.80 - 6.93 (m, 1H), 5.09 - 5.17 (m, 3H), 4.55 - 4.63 (m, 3H), 4.25 - 4.35 (m, 1H), 4.08 - 4.16 (m, 1H), 3.75 - 3.79 (m, 1H), 1.49 - 1.71 (m, 3H), 0.92 - 0.96 (m, 6H)

R_f values: 0.31 (Developing Solvent A)
0.24 (Developing Solvent B)

Example 3-34

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-fluorophenyl)oxy]propylamide (Compound No. 3-34):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 0.69 g of Reference Compound No. 3-27 synthesized in Reference Example 3-27, whereby 0.66 g of the captioned Compound No. 3-34 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.65 (s, 1H), 7.28 - 7.37 (m, 5H), 7.02 - 7.10 (m, 3H), 6.88 - 6.95 (m, 2H), 5.10 - 5.22 (m, 1H), 5.08 (s, 2H), 4.57 - 4.61 (m, 1H), 4.22 - 4.30 (m, 1H), 4.05 - 4.13 (m, 2H), 2.32 - 2.50 (m, 2H), 1.50 - 1.72 (m, 3H), 0.91 - 0.95 (m, 6H)

R_f values: 0.26 (Developing Solvent A)
0.19 (Developing Solvent B)

Example 3-35

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(3-fluorophenyl)oxy]propylamide (Compound No. 3-35):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 0.27 g of Reference Compound No. 3-28 synthesized in Reference Example 3-28, whereby 0.06 g of the captioned Compound No. 3-35 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.64 (s, 1H), 7.30 - 7.35 (m, 5H), 7.20 (q, J=8.25Hz, 1H), 6.81 - 6.88 (m, 1H), 6.54 - 6.70 (m, 3H), 5.05 - 5.12 (m, 3H), 4.56 - 4.63 (m, 1H), 4.17 - 4.27 (m, 1H), 3.96 - 4.04 (m, 2H), 2.27 - 2.54 (m, 2H), 1.45 - 1.75 (m, 3H), 0.88 - 0.95 (m, 6H)

R_f values: 0.25 (Developing Solvent A)
0.19 (Developing Solvent B)

Example 3-36

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-chlorophenyl)oxy]propylamide (Compound No. 3-36):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.05 g of Reference Compound No. 3-29 synthesized in Reference Example 3-29, whereby 0.41 g of the captioned Compound No. 3-36 was obtained.

Melting point (°C):	107.1 - 111.3
NMR (δ, $CDCl_3$):	9.70 (s, 1H), 7.33 - 7.39 (m, 5H), 7.18 - 7.23 (m, 2H), 7.06 - 7.09 (m, 1H), 6.85 - 6.94 (m, 2H), 5.17 - 5.19 (m, 1H), 5.07 (s, 2H), 4.60 - 4.64 (m, 1H), 4.26 - 4.29 (m, 1H), 4.06 - 4.10 (m, 2H), 2.42 - 2.46 (m, 2H), 1.45 - 1.75 (m, 3H), 0.90 - 0.98 (m, 6H)
R_f values:	0.27 (Developing Solvent A)
	0.20 (Developing Solvent B)

Example 3-37

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(3-chlorophenyl)oxy]propylamide (Compound No. 3-37):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.07 g of Reference Compound No. 3-30 synthesized in Reference Example 3-30, whereby 0.42 g of the captioned Compound No. 3-37 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.63 (s, 1H), 7.28 - 7.35 (m, 6H), 7.17 (t, J=8.19Hz, 1H), 6.92 - 6.95 (m, 1H), 6.85 (s, 1H), 6.72 (d, J=8.31Hz, 1H), 5.03 - 5.18 (m, 3H), 4.56 - 4.59 (m, 1H), 4.16 - 4.22 (m, 1H), 3.93 - 4.03 (m, 2H), 2.25 - 2.53 (m, 2H), 1.47 - 1.70 (m, 3H), 0.91 - 0.95 (m, 6H)
R_f values:	0.28 (Developing Solvent A)
	0.27 (Developing Solvent B)

Example 3-38

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-(1-formyl-3-benzylthio)propylamide (Compound No. 3-38):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.9 g of Reference Compound No. 3-31 synthesized in Reference Example 3-31, whereby 0.8 g of the captioned Compound No. 3-38 was obtained.

Melting point (°C):	72.8 - 81.8
NMR (δ, $CDCl_3$):	9.49 (d, J=5.76Hz, 1H), 7.24 - 7.33 (m, 10H), 6.67 - 6.69 (m, 1H), 5.14 - 5.18 (m, 1H), 5.10 (s, 2H), 4.55 - 4.64 (m, 1H), 4.15 - 4.21 (m, 1H), 3.66 (s, 2H), 2.39 - 2.43 (m, 2H), 2.11 - 2.20 (m, 1H), 1.82 - 1.90 (m, 1H), 1.47 - 1.69 (m, 3H), 0.92 - 0.95 (m, 6H)
R_f values:	0.52 (Developing Solvent A)
	0.25 (Developing Solvent B)

Example 3-39

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-fluorobenzyl)thio]propylamide (Compound No. 3-39):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.6 g of Reference Compound No. 3-32 synthesized in Reference Example 3-32, whereby 1.3 g of the captioned Compound No. 3-39 was obtained.

Melting point (°C):	99.6 - 101.0
NMR (δ, $CDCl_3$):	9.54 (s, 1H), 7.19 - 7.37 (m, 7H), 6.67 - 6.69 (m, 1H), 5.11 (s, 2H), 5.10 - 5.15 (m,

1H), 4.50 - 4.54 (m, 1H), 4.18 - 4.23 (m, 1H), 3.70 (s, 2H), 2.45 - 2.48 (m, 2H), 2.18 - 2.30 (m, 2H), 1.86 - 1.97 (m, 2H), 1.48 - 1.72 (m, 3H), 0.95 (d, J=6.24Hz, 6H)

R_f values: 0.51 (Developing Solvent A)
0.24 (Developing Solvent B)

Example 3-40

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-chlorobenzyl)thio]propylamide (Compound No. 3-40):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.2 g of Reference Compound No. 3-33 synthesized in Reference Example 3-33, whereby 0.72 g of the captioned Compound No. 3-40 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.53 (d, J=6.46Hz, 1H), 7.30 - 7.38 (m, 7H), 7.16 - 7.25 (m, 2H), 6.73 - 6.75 (m, 1H), 5.20 (d, J=7.81Hz, 1H), 5.10 (s, 2H), 4.47 - 4.53 (m, 1H), 4.18 - 4.24 (m, 1H), 3.80 (s, 2H), 2.47 - 2.52 (m, 2H), 2.16 - 2.24 (m, 1H), 1.88 - 1.94 (m, 1H), 1.48 - 1.68 (m, 3H), 0.92 - 0.94 (m, 6H)

R_f values: 0.29 (Developing Solvent A)
0.26 (Developing Solvent B)

Example 3-41

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-fluorophenyl)thio]propylamide (Compound No. 3-41):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.35 g of Reference Compound No. 3-34 synthesized in Reference Example 3-34, whereby 0.96 g of the captioned Compound No. 3-41 was obtained as an oily material.

NMR (δ, $CDCl_3$): 9.54 (d, J=6.73, 1H), 7.31 - 7.40 (m, 5H), 7.22 - 7.29 (m, 2H), 7.03 - 7.12 (m, 1H), 5.17 (d, J=7.81Hz, 1H), 5.11 (s, 1H), 4.55 - 4.60 (m, 1H), 4.20 - 4.30 (m, 1H), 2.89 - 2.94 (m, 2H), 2.10 - 2.20 (m, 1H), 1.84 - 1.95 (m, 1H), 1.49 - 1.73 (m, 3H), 0.93 - 0.96 (m, 6H)

R_f values: 0.42 (Developing Solvent A)
0.40 (Developing Solvent B)

Example 3-42

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(2-chlorophenyl)thio]propylamide (Compound No. 3-42):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.25 g of Reference Compound No. 3-35 synthesized in Reference Example 3-35, whereby 0.58 g of the captioned Compound No. 3-42 was obtained.

Melting point (°C): 109.5 - 149.0 (dec.)

NMR (δ, $CDCl_3$): 9.54 (s, 1H), 7.12 - 7.40 (m, 9H), 6.62 - 6.85 (m, 1H), 5.09 - 5.15 (m, 3H), 4.54 - 4.60 (m, 1H), 4.21 - 4.25 (m, 1H), 2.94 - 3.00 (m, 2H), 2.27 - 3.40 (m, 1H), 1.90 - 2.02 (m, 1H), 1.49 - 1.71 (m, 3H), 0.93 - 0.95 (m, 6H)

R_f values: 0.27 (Developing Solvent A)
0.27 (Developing Solvent B)

Example 3-43

Synthesis of L-N-benzyloxycarbonylleucine-(2S)-[1-formyl-3-(4-chlorophenyl)thio]propylamide (Compound No. 3-43):

The same reaction procedure as used in Example 3-21 was repeated except that the 4 g of Reference Compound No. 3-16 synthesized in Reference Example 3-16 was replaced by the 1.58 g of Reference Compound No. 3-38 synthesized in Reference Example 3-38, whereby 0.71 g of the captioned Compound No. 3-43 was obtained as an oily material.

NMR (δ, $CDCl_3$):	9.52 (d, J=7.21Hz, 1H), 7.32 (s, 5H), 7.25 (s, 4H), 6.72 - 6.90 (m, 1H), 5.14 - 5.17 (m, 1H), 5.10 (d, J=4.88Hz, 2H), 4.53 - 4.60 (m, 1H), 4.15 - 4.25 (m, 1H), 2.88 - 2.93 (m, 2H), 2.20 - 2.35 (m, 1H), 1.82 - 1.98 (m, 1H), 1.49 - 1.68 (m, 3H), 0.93 - 0.98 (m, 6H)
R_f values:	0.30 (Developing Solvent A)
	0.30 (Developing Solvent B)

Test Example 1 Measurement of Calpain Inhibiting Effect

Calpain was separated from a skeletal muscle of a Japanese white rabbit and partially purified according to the method of Tsuji and Imahori as described in J.Biochem. 90, 233-240 (1981), whereby the calpain for use in a test for investigating the calpain inhibiting effect (i.e., the inhibitory effect on calpain activity) of the aldehyde compounds according to the present invention was prepared.

The calpain inhibiting effect was measured in accordance with the method of Yoshimura et al. as described in J. Biol. Chem. 258, 8883-8889 (1983).

Each assay mixture was prepared by mixing 0.05 ml of a 4% casein solution, 0.05 ml of a 50 mM cysteine solution, 0.05 ml of a calpain solution, 0.025 ml of purified water, 0.025 ml of a 10% dimethyl sulfoxide solution containing each compound shown in Table 15 and 0.25 ml of a 200 mM imidazole hydrochloric acid buffer solution (pH=7.5).

The thus prepared assay mixture was preincubated at 30°C for 3 minutes. The reaction was started by the addition of 0.05 ml of a 50 mM calcium chloride solution to the above mixture. After the incubation at 30°C for 30 minutes, the reaction was terminated by the addition of 0.5 ml of 5% trichloroacetic acid.

The amount of a trichloroacetic-acid-soluble protein produced by hydrolysis of casein by calpain was measured by the spectrophotometric analysis in accordance with the method of Ross and Schatz as described in Anal. Biochem. 54, 304-306 (1973), and the absorbance (a) of each sample was measured.

The absorbance (b) of a blank sample which was treated similarly without any of the aldehyde compounds of the present invention, dissolved in a 10% dimethyl sulfoxide solution, was measured.

The inhibition of calpain activity was calculated in accordance with the formula [(b-a)/b] X 100, and the amount of each aldehyde compound necessary to inhibit calpain activity by 50% [IC_{50}] was calculated according to the method of Probit. The results are shown in Table 15.

Table 15

Compound No. in Example	Calpain Inhibiting Effect [IC_{50}] (μM)	Compound No. in Example	Calpain Inhibiting Effect [IC_{50}] (μM)
1-1	6.6	2-3	1.60
1-7	3.0	2-4	2.40
1-26	0.89	2-13	1.23
1-27	0.75	2-14	1.90
1-28	0.22	2-17	3.60
1-30	1.10	2-18	0.58
1-32	2.00	2-19	0.59
1-34	0.17	2-20	4.40
1-36	0.78	2-21	2.00
1-38	1.90	2-22	3.30
1-39	2.30	3-41	0.27
1-41	0.94	3-42	0.44
1-42	0.35	3-43	0.52
1-43	0.56	3-44	0.95
1-44	0.99	3-45	0.62
1-51	1.40	3-46	0.61
1-55	0.63	3-47	2.00
1-58	0.68	3-48	1.50
1-61	0.88	3-49	0.85
1-62	1.60	3-50	0.22

Table 15

Compound No. in Example	Calpain Inhibiting Effect $[IC_{50}]$ (μM)	Compound No. in Example	Calpain Inhibiting Effect $[IC_{50}]$ (μM)
3-51	0.32	3-70	0.30
3-52	0.90	3-71	0.22
3-53	1.30	3-72	0.20
3-54	1.30	3-73	0.43
3-55	0.70	3-74	0.42
3-61	0.41	3-75	0.17
3-62	0.44	3-76	0.14
3-63	0.99	3-77	0.19
3-64	0.29	3-78	0.14
3-65	1.20	3-79	0.11
3-66	1.20	3-80	0.33
3-67	0.61	3-81	0.58
3-68	1.30	3-82	1.21
3-69	0.47	3-83	0.51

Test Example 2 Measurement of Platelet-aggregation Inhibiting Effect

Platelet rich plasma (PRP) was prepared and the platelet aggregation was measured in accordance with the method of Born and Cross as described in J. Physiol. 168, 178-195 (1963).

Blood of a Japanese white rabbit was drawn from a carotid artery of the rabbit. 9 parts by volume of the blood were mixed with 1 part by volume of a 3.8% aqueous solution of sodium citrate. The mixture was immediately centrifuged at 200 x g at 20°C for 15 minutes, and PRP was obtained in the supernate. The number of platelets was calculated by use of an electronic cell counter (MEK-4150 manufactured by Nihon Kohden Kabushiki Kaisha). PRP with 55 X 10^4 or more platelets per 1 μl was employed in the tests.

10 μl of a test solution containing any of the aldehyde compounds of the present invention was added to 200 μl of PRP. The mixture was preincubated at 37°C for 5 minutes. To this mixture, 10 μl of collagen (22 μg/ml) was added to cause the aggregation. The aggregation was measured by Agricometer (NKK, PAT-4A).

In preparing the above test solution, each compound synthesized in the previously mentioned Examples as shown in Table 16 was dissolved in combined dimethyl sulfoxide and polyoxyethylene 60 hardened castor oil in ethanol. The mixture was diluted with an isotonic saline and the final concentration of the dimethyl sulfoxide and polyoxyethylene 60 hardened castor oil contained in the above mixture was adjusted to less than 1%.

The inhibitory activity of each aldehyde compound on platelet aggregation was expressed by percentages compared with a blank test defined as 100% which was performed without any of the aldehyde compounds.

The amount of each aldehyde compound necessary to inhibit the platelet aggregation by 50% $[IC_{50}]$ was calculated according to the method of Probit. The results are shown in Table 16.

Table 16

Compound No. in Example	Platelet Aggregation Inhibiting Activity [IC_{50}] (μM)	Compound No. in Example	Platelet Aggregation Inhibiting Activity [IC_{50}] (μM)
1-27	2.90	3-50	25.0
1-42	23.0	3-51	88.0
1-44	47.0	3-52	61.0
1-51	10.0	3-55	44.0
1-58	22.0	3-61	9.40
1-61	9.60	3-62	21.0
1-62	17.0	3-63	23.0
2-19	4.20	3-64	28.0
2-27	65.0	3-67	18.0
3-41	58.0	3-69	13.0
3-42	94.0	3-70	9.60
3-43	52.0	3-72	54.0
3-44	60.0	3-73	9.20
3-45	56.0	3-76	11.0
3-48	83.0	3-83	28.0

Test Example 3 Measurement of Inhibitory Effect on Protease other than Calpain

(1) Measurement of Inhibitory Effect on Trypsin Activity

The inhibitory effect on trypsin activity was measured by a partially modified method of Aoyagi as described in J. Antibiotics, 22, 558-568 (1969).

An assay mixture was prepared by mixing 0.5 ml of a 2% casein solution, 0.05 ml of a 50 mM calcium chloride solution, 0.05 ml of a 10% dimethyl sulfoxide solution containing each of Compounds No. 3-61, 3-63, 3-76 and 3-83, 0.1 ml of purified water and 0.25 ml of a 70 mM boric acid buffer solution (pH = 7.4).

The assay mixture was preincubated at 37°C for 3 minutes, and the reaction was started by the addition of 0.05 ml of 0.1 mg/ml trypsin to the above mixture. After incubation at 37°C for 30 minutes, the reaction was terminated by the addition of 1 ml of 1.7 N perchloric acid. After allowing the reaction mixture to stand for 60 minutes, the mixture was centrifuged at 3000 rpm for 10 minutes. The absorbance (a) of the supernate was measured at 280 nm.

The absorbance (b) of a blank sample which was treated similarly, without any aldehyde compound, dissolved in 10% dimethyl sulfoxide, was measured. The inhibition of trypsin activity was calculated in accordance with the formula [(b-a)] X 100.

None of the above compounds showed inhibitory effect at a concentration of 10^{-5} M.

(2) Measurement of Inhibitory Effect on α-Chymotrypsin

The inhibitory effect on α-chymotrypsin was measured by a partially modified method of Erlanger, B. F. as described in Ach. Biochem. Biophys. 115, 206-210 (1966).

An assay mixture was prepared by mixing 0.05 ml of 10 mM glutaryl-L-phenylalanine-p-nitroanilide dissolved in dimethyl sulfoxide and polyoxyethylene 60 hardened castor oil, 0.1 ml of a 50 mM calcium chloride solution, 0.25 ml of purified water, 0.05 ml of a compound to be tested dissolved in combined dimethyl sulfoxide and polyoxyethylene 60 hardened castor oil, and 0.5 ml of 100 mM trishydrochloric acid buffer solution (pH = 7.8).

The mixture was preincubated at 25°C for 3 minutes. To the above mixture, and the reaction was started by the addition of 0.05 ml of 2 mg/ml α-chymotrypsin. The increase of 405 nm absorbance was measured at 25°C with time, and the transition rate (a) of the absorbance per min was calculated.

The rate (b) of the absorbance of a blank sample treated similarly without any compound dissolved in combined dimethyl sulfoxide and 10% polyoxyethylene 60 hardened castor oil was measured. The inhibition of α-chymotrypsin activity was calculated in accordance with the formula [(b-a)/b] X 100, and the amount of each compound necessary to inhibit α-chymotrypsin activity by 50% [IC_{50}] was calculated according to the method of Probit.

The inhibitory effect of SUAM-14541, a compound disclosed in Japanese Laid-Open Patent Application 1-121257, on α-chymotrypsin activity was measured for comparison.

The results are shown in Table 17.

Table 17

Compound tested	Inhibitory Effect [IC_{50}]
Compound No. 3-6	>10^{-4}M
SUAM-14541	2.1 X 10^{-5}M

The aldehyde derivatives according to the present invention are useful for treatment of inveterate diseases such as ischemic diseases, inflammation, progressive muscular dystrophy, cataracts, and hypoimmunity as shown in the above Test Examples since the derivatives have excellent capabilities for inhibiting calpain activity.

The derivatives can be administered perorally, intravenously, hypodermically or intramuscularly. Therefore, the derivatives can be used in various administration forms including pellets, capsules, liquids, and suppositories.

Claims

1. Aldehyde derivatives represented by formula (I):

$$\text{Z-CONH-}\underset{}{\overset{\text{CHO}}{\overset{|}{\text{CH}}}}\text{-(CH}_2)_n\text{-R}^1 \qquad \text{(I)}$$

wherein R^1 represents an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group, a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, or a group of $-X-R^3$ in which X represents O, $-S(O)_m-$ (m = 0, 1, or 2), and R^3 represents an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group, a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group, or an alkyl group having 1 to 10 carbon atoms; Z represents R^4-Y- or R^6O-CH(R^5)- in which Y represents a 3- to 7-membered nitrogen-containing saturated heterocyclic group selected from the group consisting of aziridine, azetidine, pyrrolidine, piperidine and perhydroazepine, or a monocyclic saturated hydrocarbon group having 3 to 7 carbon atoms selected from the group consisting of cyclopropane, cyclobutane, cyclopentane and cycloheptane, R^4 represents an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an acyl group selected from the group consisting of acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cyclohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluoyl group, 1-(benzyloxycarbonyl)piperidine-4-carbonyl group, cinnamoyl group, phenylacetyl group, 2-thienylcarbonyl group, trimethyl acetyl group, cyclopentane carbonyl group, 2,6-dichloro benzoyl group, 3,4-dichlorobenzoyl group, 4-phenyl benzoyl group, 2-chlorocinnamoyl group, 3-chlorocinnamoyl group, 4-chlorocinnamoyl group, 2-nitrocinnamoyl group,

indolyl-2-carbonyl group, indolyl-3-carbonyl group, quinolyl-2-carbonyl group, quinolyl-3-carbonyl group, isoquinolyl-3-carbonyl group, diphenylacetyl group, fluorenyl-9-carbonyl group, 3-phenylpropionyl group, 4-phenyl-butyryl group, 3-(3-pyridyl)acryloyl group, 3-(3-thienyl)acryloyl group, 3-phenyl-2-methylacryloyl group, 3-(2-naphthyl)acryloyl group, (2S)-3-phenyl-2-(benzyloxycarbonylamino)propionyl group, and (2R)-3-phenyl-2-(benzyloxycarbonylamino)propionyl group, a sulfonyl group selected from the group consisting of methane sulfonyl group, ethane sulfonyl group, propane sulfonyl group, butane sulfonyl group, pentane sulfonyl group, hexane sulfonyl group, trifluoromethane sulfonyl group, benzene sulfonyl group, naphthalene-2-sulfonyl group, 4-methyl benzene sulfonyl group, iso-quinoline-5-sulfonyl group, and quinoline-8-sulfonyl group, an alkoxycarbonyl group selected from the group consisting of methoxy carbonyl group, ethoxy carbonyl group, propoxy carbonyl group, butoxy carbonyl group, pentyloxy carbonyl group, hexyloxy carbonyl group, heptyloxy carbonyl group, octyloxy carbonyl group, nonyloxy carbonyl group, decyloxy carbonyl group, iso-propoxy carbonyl group, iso-butoxy carbonyl group, s-butoxy carbonyl group, t-butoxy carbonyl group, iso-pentyloxy carbonyl group, neopentyloxy carbonyl group, t-pentyloxy carbonyl group, iso-hexyloxy carbonyl group, cinnamyloxy carbonyl group, and benzyloxy carbonyl group, a carbamoyl group selected from the group consisting of N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)-carbamoyl group, N-(3-chlorophenyl)carbamoyl group, N-(4-chlorophenyl)carbamoyl group, N-(1-naphthyl)carbamoyl group, N-(2-naphthyl)carbamoyl group,and N-benzylcarbamoyl group, or a thiocarbamoyl group selected from the group consisting of N-methylthiocarbamoyl group, N-ethylthiocarbamoyl group, N-phenylthiocarbamoyl group, N-(2-chlorophenyl)thiocarbamoyl group, N-(1-naphthyl)-thiocarbamoyl group, N-(2-naphthyl)thiocarbamoyl group, and N-benzylthiocarbamoyl group, R^5 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group, and R^6 represents an acyl group selected from the group consisting of acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cyicohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluoyl group, and 1-(benzyloxycarbonyl)-piperidine-4-carbonyl group, a carbamoyl group selected from the group consisting of N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)carbamoyl group, N-(2-naphthyl)carbamoyl group and N-benzylcarbamoyl group, a thiocarbamoyl group selected from the group consisting of N-methylthiocarbamoyl group, N-ethylthiocarbamoyl group, N-phenylthiocarbamoyl group, N-(2-chlorophenyl)thiocarbamoyl group, N-(1-naphthyl)thiocarbamoyl group and N-benzylthiocarbamoyl group, or an alkyl group having 1 to 10 carbon atoms; and n is an integer of 1 to 5.

2. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

3. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

4. The aldehyde derivatives as claimed in Claim 1, wherein said alkenyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

5. The aldehyde derivatives as claimed in Claim 1, wherein said alkenyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

6. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^3 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

7. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^3 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

8. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^1 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

9. The aldehyde derivatives as claimed in Claim 8, wherein said alkyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

10. The aldehyde derivatives as claimed in Claim 8, wherein said alkyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

11. The aldehyde derivative as claimed in Claim 1, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^1 is selected from the group consisting of ethenyl group, 1-propenyl group, 2-propenyl group, iso-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-2-propenyl group, 1-pentenyl group, 1-hexenyl group, 1-heptenyl group, 1-cyclohexenyl group, 2-cylcohexenyl group, aromatic hydrocarbon, and heterocyclic group.

12. The aldehyde derivatives as claimed in Claim 11, wherein said alkenyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

13. The aldehyde derivatives as claimed in Claim 11, wherein said alkenyl group having 1 to 10 carbon atoms represented by R^1 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

14. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^3 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

15. The aldehyde derivatives as claimed in Claim 14, wherein said alkyl group having 1 to 10 carbon atoms represented by R^3 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

16. The aldehyde derivatives as claimed in Claim 14, wherein said alkyl group having 1 to 10 carbon atoms represented by R^3 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

17. The aldehyde derivagive as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

18. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

19. The aldehyde derivagive as claimed in Claim 1, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

20. The aldehyde derivatives as claimed in Claim 1, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl

group.

21. The aldehyde derivagive as claimed in Claim 1, wherein said alkynyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

22. The aldehyde derivatives as claimed in Claim 1, wherein said alkynyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

23. The aldehyde derivatives as claimed in Claim 1, wherein said alkyl group having 1 to 10 carbon atoms represented by R^4 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

24. The aldehyde derivagive as claimed in Claim 23, wherein said alkyl group having 1 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

25. The aldehyde derivatives as claimed in Claim 23, wherein said alkyl group having 1 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

26. The aldehyde derivatives as claimed in Claim 1, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^4 is selected from the group consisting of vinyl group, 1-propenyl group, 2-propenyl group, iso-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-2-propenyl group, 1-pentenyl group, 1-hexenyl group, 1-heptenyl group, 1-cyclohexenyl group and 2-cyclohexenyl group.

27. The aldehyde derivagive as claimed in Claim 26, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

28. The aldehyde derivatives as claimed in Claim 26, wherein said alkenyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

29. The aldehyde derivatives as claimed in Claim 1, wherein said alkynyl group having 2 to 10 carbon atoms represented by R^4 is selected from the group consisting of 1-propynyl group, 2-propynyl group, 1-butynyl group, 2-butynyl group, 1-pentynyl group, 1-hexynyl group, 1-heptynyl group, 1-optynyl group, 1-nonyl group, 1-denyl group and 1-methyl-2-propynyl group.

30. The aldehyde derivagive as claimed in Claim 29, wherein said alkynyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

31. The aldehyde derivatives as claimed in Claim 29, wherein said alkynyl group having 2 to 10 carbon atoms represented by R^4 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

32. The aldehyde derivatives as claimed in Claim 1, wherein said aromatic hydrocarbon group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group,

a hydroxyl group and a nitro group.

33. The aldehyde derivatives as claimed in Claim 1, wherein said heterocyclic group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

34. The aldehyde derivatives as claimed in Claim 2, wherein said aromatic hydrocarbon group which is a substituent of said alkyl group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

35. The aldehyde derivatives as claimed in Claim 3, wherein said heterocyclic group which is a substituent of said alkyl group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

36. The aldehyde derivatives as claimed in Claim 4, wherein said aromatic hydrocarbon group which is a substituent of said alkenyl group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

37. The aldehyde derivatives as claimed in Claim 5, wherein said heterocyclic group which is a substituent of said alkenyl group represented by R^1 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

38. Aldehyde derivatives represented by formula (II):

$$\begin{array}{c}
\phantom{R^{10}-}\overset{R^9}{}\overset{R^8}{}\overset{CHO}{} \\
R^{10}-\underset{}{\overset{|}{N}}-\overset{|}{C}H-CONH-\overset{|}{C}H-(CH_2)_n-X-R^7
\end{array}$$

wherein R^7 represents an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group, a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group, an alkyl group having 1 to 10 carbon atoms with a substituent selected from phenyl group, naphthyl group, anthranyl group, furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group, or a cyclic alkyl group having 3 to 8 carbon atoms; R^8 represents hydrogen, an alkyl group having 1 to 10 carbon atoms, or an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group; R^9 represents hydrogen, or an alkyl group having 1 to 10 carbon atoms; R^{10} represents an alkoxycarbonyl group selected from the group consisting of methoxy carbonyl group, ethoxy carbonyl group, propoxy carbonyl group, butoxy carbonyl group, pentyloxy carbonyl group, hexyloxy carbonyl group, heptyloxy carbonyl group, octyloxy carbonyl group, nonyloxy carbonyl group, decyloxy carbonyl group, iso-propoxy carbonyl group, iso-butoxy carbonyl group, s-butoxy carbonyl group, t-butoxy carbonyl group, iso-pentyloxy carbonyl group, neopentyloxy carbonyl group, t-pentyloxy carbonyl group, iso-hexyloxy carbonyl group, cinnamyloxy carbonyl group, and benzyloxy carbonyl group, an acyl group selected from the group consisting of acetyl group, propionyl group, butyryl group, valeryl group, hexanoyl group, heptanoyl group, iso-valeryl group, cylcohexane carbonyl group, benzoyl group, 1-naphthoyl group, 2-naphthoyl group, toluyl group, and 1-(benzyloxycarbonyl)piperidine-4-carbonyl group, a car-

bamoyl group selected from the group consisting of N-methylcarbamoyl group, N-ethylcarbamoyl group, N-phenylcarbamoyl group, N-(2-chlorophenyl)carbamoyl group, N-(2-naphthyl)carbamoyl group and N-benzylcarbamoyl group, or a sulfonyl group selected from the group consisting of methane sulfonyl group, ethane sulfonyl group, propane sulfonyl group, butane sulfonyl group, pentane sulfonyl group, hexane sulfonyl group, trifluoromethane sulfonyl group, benzene sulfonyl group, naphthalene sulfonyl group, 4-methyl benzene sulfonyl group, iso-quinoline-5-sulfonyl group, and quinoline-8-sulfonyl group; X represents oxygen, or a group represented by $-S(O)_m-$ in which m is 0, 1 or 2; and n is an integer of 1 to 5.

39. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group having 1 to 10 carbon atoms represented by R^7 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

40. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group having 1 to 10 carbon atoms represented by R^8 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

41. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group having 1 to 10 carbon atoms represented by R^9 is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

42. The aldehyde derivatives as claimed in Claim 38, wherein said aromatic hydrocarbon group represented by R^7 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

43. The aldehyde derivatives as claimed in Claim 38, wherein said heterocyclic group represented by R^7 has a substituent selected from the group consisting of an alkyl group having 1 to 10 carbon atoms, an alkoxyl group having 1 to 10 carbon atoms, a halogen selected from the group consisting of fluorine, chlorine, bromine and iodine, an amino group, a dimethyl amino group, a diethyl amino group, a hydroxyl group and a nitro group.

44. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group represented by R^8 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

45. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group represented by R^8 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

46. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group represented by R^9 has as a substituent an aromatic hydrocarbon group selected from the group consisting of phenyl group, naphthyl group and anthranyl group.

47. The aldehyde derivatives as claimed in Claim 38, wherein said alkyl group represented by R^9 has as a substituent a heterocyclic group selected from the group consisting of furyl group, thienyl group, pyrrolyl group, pyridyl group, quinolyl group, isoquinolyl group, and indolyl group.

48. The aldehyde derivatives as claimed in Claim 42, wherein said alkyl group having 1 to 10 carbon atoms is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl

group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

49. The aldehyde derivatives as claimed in Claim 43, wherein said alkyl group having 1 to 10 carbon atoms is selected from the group consisting of methyl group, ethyl group, propyl group, butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, iso-propyl group, s-butyl group, t-butyl group, iso-pentyl group, neopentyl group, t-pentyl group, iso-hexyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, and cyclohexyl group.

50. The aldehyde derivatives as claimed in Claim 42, wherein said alkoxyl group having 1 to 10 carbon atoms is selected from the group consisting of methoxy group, ethoxy group, propoxy group, butoxy group, pentyloxy group, hexyloxy group, butyloxy group, octyloxy group, nonyloxy group, decyloxy group, iso-propoxy group, iso-butoxy group, s-butoxy group, t-butoxy group, iso-pentyloxy group, neopentyloxy group, t-pentyloxy group and iso-hexyloxy group, and benzyloxy group.

51. The aldehyde derivatives as claimed in Claim 43, wherein said alkoxyl group having 1 to 10 carbon atoms is selected from the group consisting of methoxy group, ethoxy group, propoxy group, butoxy group, pentyloxy group, hexyloxy group, butyloxy group, octyloxy group, nonyloxy group, decyloxy group, iso-propoxy group, iso-butoxy group, s-butoxy group, t-butoxy group, iso-pentyloxy group, neopentyloxy group, t-pentyloxy group and iso-hexyloxy group, and benzyloxy group.